GENETIC SCREENING IN THE WORKPLACE

HEARING

BEFORE THE

SUBCOMMITTEE ON
INVESTIGATIONS AND OVERSIGHT

OF THE

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SCIENCE AND TECHNOLOGY
U.S. HOUSE OF REPRESENTATIVES

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*On assignment to Budget Committee for 97th Congress.

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GENETIC SCREENING IN THE WORKPLACE

WEDNESDAY, OCTOBER 6, 1982

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE AND TECHNOLOGY,
SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT,
Washington, D.C.

The subcommittee met, pursuant to call, at 9:30 a.m., in room 2325, Rayburn House Office Building, Hon. Albert Gore, Jr. (chairman of the subcommittee), presiding.

Mr. GORE. The subcommittee will come to order.

I would like to welcome our guests and our witnesses. Ever since the advent of recombinant DNA technologies, our society has been both troubled and excited by the new potentials they create; by being able to analyze and manipulate the human cell, science will become capable of miracles, but it can also create nightmares.

An equally sensitive public issue has been workers' exposure to toxic chemicals and substances. As our knowledge base increases, we are now aware of more than 55,000 chemicals in the workplace; and our knowledge of those that are harmful is increasing almost exponentially. As concern grows for the health of workers, employers are naturally becoming more and more sensitive to the liability considerations posed by occupational illnesses. We are all aware of last month's events with the Manville Corp., which claimed that their potential financial exposure has driven them to bankruptcy.

The topic we will consider today deals with both of these issues.

Last year, in an effort to get more accurate information on this subject, the subcommittee asked the Office of Technology Assessment to undertake a comprehensive study of genetic screening in the workplace, in order to lend us some guidance on the public policy implications of such a technology.

A major component of that study was to determine how prevalent such testing methods really were. It was frankly our impression at the time that this was an issue that would probably face the legislators of our children's generation.

However, the OTA survey, which was presented in testimony before this subcommittee last June, surprised us all. Among the Fortune 500 companies polled, a handful were already utilizing genetic testing techniques, and some 59 companies indicated they were entertaining plans of doing so in the near future. This means that such practices are a near-term reality, not merely a topic to be considered in the future; and they represent a knotty set of issues that Congress will have to solve sooner rather than later.

Our past inquiries have addressed the scientific issues and the potential legal impacts of genetic screening. Today, we will begin a

new area for examination, the ethical implications. While ethics is normally considered to be a somewhat academic subject, it is not the case here. Because there are few legal precedents on this new issue, the thoughts of ethicists will be valuable to any congressional or public deliberation.

We will also hear from some scientists who are investigators in the field of genetic screening, one of whom will describe a new testing technique just developed. As well, we will hear from a scientist who is more skeptical about the potential of such tests.

Finally, the Office of Technology Assessment will report on their year-long study of this issue, and will offer us their guidance.

We appreciate the time and effort of all the witnesses in assisting Congress in its effort to wrestle with such issues. Genetic screening is an example of how technology is becoming increasingly capable of straining our sociopolitical institutions. Nevertheless, many of the hard choices ahead will fall to Congress, and for that reason, we appreciate the work you have done and the views that you are presenting here today.

[The opening statement of Representative Walker follows:]

OPENING STATEMENT OF U.S. REPRESENTATIVE ROBERT S. WALKER

Good morning Mr. Chairman, I would like to join you in a warm welcome to our witnesses here today. As you already know, the original schedule of the House was to be in session this week. Because of a sudden change last week, we are now in recess, and most Members have returned to their districts to attend to the important business of the campaign trail.

Our topic is one which is of great interest to the Chariman, but it is also one which should be of interest to all members of the Committee.

Genetic screening, if it was error free, would be a powerful tool to reduce the hazard of the workplace, and thus to reduce the degree of risk facing millions of Americans each day. But we know that genetic screening is not fool-proof. We know that there is a real difference between genetic testing and genetic monitoring, and that monitoring for radiation damage is fairly accurate. However, there should be serious concern when we hear that both biochemical and cytogenic tests have, at best, little predictive value at the present.

As in many areas of developing science, we find that many of the proponents of these tests are doing the very research which may eventually provide a sufficient scientific data base to ensure that the tests they champion are validated. But to use these tests at the present to make decisions on hiring or job retention must raise some serious legal and ethical questions.

Briefly stated, genetic screening is a process in which blood is taken from the subject for the purpose of examing the genes in the blood in order to identify individuals who are more likely to contract a particular disease as a result of exposure to certain chemicals or substances in the workplace.

The problem which we hope to address today is how these tests can be utilized with any confidence when we are faced with great gaps in our most basic understanding of how the disease process works within the human body.

There is no doubt that the business world is far more sensitive today to the potential reaction of the public when the company may be found responsible for causing harm. Only a few short weeks age, a major producer of asbestos filed for bankruptcy as a result of literally thousands of claims already filed against it is the courts by workers exposed to asbestos.

But society needs to be assured that if tests are adopted, that they are reasonable and accurate and have a proper relationship to the risks involved.

Today, we will hear from a number of witnesses who, hopefully, will shed some light on the topic.

Mr. GORE. Before calling our first witnesses, I would like to call on the ranking member of the subcommittee, Mr. Shamansky of Ohio.

Mr. SHAMANSKY. Thank you, Mr. Chairman. The hearings that this committee has held on genetic screening have seized the attention of some of my constituents, as is evidenced by an editorial comment in the Columbus Citizen-Journal, dated September 6, 1982.

Surely, the ethical and scientific aspects of genetic screening can only blossom as an area of inquiry, concern, and progress in preventing illness to workers and their children.

In addition to this intellectual concern, Mr. Chairman, my constituents and I have a great economic interest in the development of high-technology firms, especially those located in the Columbus area. Dr. Philip Lipetz—who will be testifying later—represents a firm which is part of the dynamic high-technology base in Columbus. In addition, I am pleased to say that Dr. Howard Sloan of the Department of Pediatrics, College of Medicine of Ohio State University, the children's hospital represents the body of research being conducted in central Ohio.

Clearly, Columbus, Ohio, is now and will continue to be a center for scientific and high-technology enterprise. Last year, the Science, Research and Technology Subcommittee, of which I am a member, held a field hearing in Columbus, focusing on the "Local Incentives for High-Technology Firms and Innovation."

Columbus' high-technology base springs from governmental, educational, and research establishments, as well as smaller entrepreneurs and other businesses. We are determined that the future of our country as well as our particular area is intimately connected with this sort of endeavor, and this is another aspect of the concern that the whole country must have in such enterprises.

Columbus has shown intellectual and economic interest in today's topic. Thus, it is appropriate that the committee extended an invitation to both Dr. Philip Lipetz and Dr. Sloan, and I greatly appreciate and value these hearings.

Thank you very much.

Mr. GORE. Thank you, and thank you for all the work you have done on this issue.

Our first two witnesses are Geoffrey Karny, project director of the biological applications program at the Office of Technology Assessment here in Washington, and accompanied by Dr. Nan Newell, a senior analyst with the biological applications program.

If you two would come forward to the witness table. Let me thank you for coming here today. Let me ask unanimous consent—I should have done this earlier—without objection, the opening statement of the ranking minority member, Mr. Walker, will be included in the record just after my opening statement.

And he may join us a little bit later on. It is a difficult time for Members of Congress as some of you may know. We had scheduled this hearing at a time when we thought the Congress was going to be in session this week, but Congress adjourned a little bit early, a week early, and we decided to go ahead with the hearing so as not to inconvenience the witnesses and because of the import of the subject under investigation. So the absence of some of our colleagues will I hope be understandable to you.

Mr. Karny, I want to thank you and Dr. Newell for all the work that you all have done at the Office of Technology Assessment.

OTA as we refer to it was set up in order to assist the Congress in understanding the impact of new technologies that are created. We have learned painfully in this century that new technologies can sometimes sweep aside social, political conventions and institutions without us really being fully aware of that impact until a lot of changes have already occurred, and the realization that we needed to do a better job in predicting and understanding those impacts was what led to the creation of OTA, and I think your work on genetic screening is certainly a fine example of how your institution has fulfilled the promise that led to its creation.

Mr. Karny, without objection, your entire statement will be included in the record, and we invite you to proceed with it at this time.

[The biographical sketch of Mr. Karny follows:]

BIOGRAPHICAL SKETCH

Geoffrey M. Karny

PROFESSIONAL EXPERIENCE:

ATTORNEY, U.S. CONGRESS, OFFICE OF TECHNOLOGY ASSESSMENT, Washington, D.C.
December 1979 - Present

Project Director, OTA Assessment of The Role of Genetic Testing in the Prevention of Occupational Illness (October 1981 - Present)

Staff Attorney, OTA Assessment of U.S. International Competitiveness in Biotechnology (October 1981 - Present)

Staff Attorney, OTA Assessment of Impacts of Applied Genetics: Microorganisms, Plants, and Animals (December 1979 - September 1981).

ATTORNEY, U.S. SECURITIES AND EXCHANGE COMMISSION, Washington, D.C.
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PUBLICATONS:

Contributions to Books

"Regulation of Genetic Engineering," in Impacts of Applied Genetics: Microorganisms, Plants, and Animals, Office of Technology Assessment (Washington, D.C.: GPO 1981), pp. 211-234.

"Patenting Living Organisms," in Impacts of Applied Genetics, pp. 237-254.

"History of the Recombinant DNA Debate," in Impacts of Applied Genetics, pp. 315-319.

"Constitutional Constraints on Regulation," in Impacts of Applied Genetics, pp. 320-321.

"Revisions in Patent Law and the Patent Court System Affecting the Patenting of Life Forms," G. Bernard, N. Noonan, and G. M. Karny, in Banbury Report 10: Patenting of Life Forms (New York: Cold Spring Harbor Laboratory 1982), pp. 285-320.

Articles

"Regulation of Genetic Engineering: Less Concern about Frankensteins but Time for Action on Commercial Production," 12 U. Tol. L. Rev. 815 (1981).

"Regulation of Genetic Engineering in the Food and Agriculture Industries" 4 Recombinant DNA Tech. Bull. 152 (1981).

"Ownership Rights in Biological Inventions," Genetic Engineering News (November/December 1981), p.4.

"Recombinant DNA Guidelines and Environmental Concerns," Genetic Engineering News (March/April 1982), p.6.

"Biotechnology: The Regulatory and Legislative Environment," 5 Recombinant DNA Tech. Bull (in press).

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STATEMENT OF GEOFFREY KARNY, PROJECT DIRECTOR, BIOLOGICAL APPLICATIONS PROGRAM, OFFICE OF TECHNOLOGY ASSESSMENT, ACCOMPANIED BY NAN NEWELL, SENIOR ANALYST

Mr. KARNY. Thank you. I am pleased to appear here on behalf of OTA to present the findings of our study on the role of genetic testing in the prevention of occupational disease. Although the study is near completion, our draft report must undergo additional review and has not yet been presented to the Technology Assessment Board. Therefore, these findings should be considered preliminary and not the final findings of OTA.

The term "genetic testing" covers two inherently different kinds of procedures, genetic monitoring and genetic screening.

Genetic monitoring involves periodically examining a group of workers by collecting blood or other body fluids to assess whether genetic damage has occurred in certain cells. I emphasize the word "group" because there is no way yet to identify which individuals in the group would be at increased risk.

In contrast, genetic screening is a one-time procedure. It is to determine if a person has particular genetic traits regardless of prior exposure. Some scientists have hypothesized that these traits, which are normally not harmful, might predispose the individual to illness when he or she is exposed to particular chemicals in the workplace.

Screening has the potential to determine individual susceptibility prior to exposure, whereas monitoring may be able to identify a population that is at increased risk because of exposure to a hazardous substance. Because of this distinction, screening could be used to exclude genetically susceptible individuals from jobs where they would be exposed to hazardous substances.

Although this technology is still in its infancy, its advocates believe that it might be able to play an important role in the prevention of occupational disease. Others, however, think the techniques will be of little value and are concerned about potentially adverse impacts upon the workers and upon efforts to clean up the workplace.

An even more fundamental question arises if the tests were to become highly predictive. Then society must ask itself to what degree it desires to protect high risk individuals or groups, at what cost, and who should bear that cost.

Although it is too soon to be able to answer many of the troubling questions raised by genetic testing, it is not too soon to think about them. As we reported to you at your June 22 hearing, our survey of major companies and unions found considerable interest in the potential of genetic testing.

Since there have been no significant changes in those findings, the remainder of my remarks will concentrate on our preliminary findings on the scientific, legal, ethical, and economic issues.

With respect to the science, we took a two stage approach. We evaluated the reliability and validity of the tests themselves. Then we evaluated existing data on the correlation between either the genetic trait or the genetic damage and an increased risk for disease. Our basic conclusion is that none of the current genetic tests

meet established scientific criteria for routine use in an occupational setting. However, there is enough suggestive evidence to merit further research. I will elaborate on these points.

With respect to genetic monitoring, we found that the concept is well grounded on a theoretical and experimental base. Ionizing radiation and a wide range of chemicals can cause damage to the genetic material in experimental animals and in some cases humans. This damage may result in mutations, which are changes in the genetic information. The consequences of increasing the mutation rate in somatic cells are not well understood, but mutations have been implicated in several diseases, most importantly cancer. There are two major types of genetic monitoring methods—cytogenetic methods, which detect major structural changes in chromosomes, and noncytogenetic methods, which detect actual damage to the DNA itself.

Mr. GORE. Let me interrupt you there. When you say cytogenetic screening and noncytogenetic screening, noncytogenetic screening is what we were calling biochemical screening in the last set of hearings?

Mr. KARNY. The use of the adjective "biochemical" was an attempt to further distinguish the two different techniques. The noncytogenetic techniques seek to determine damage to DNA directly, and they are a type of monitoring technique. In the last hearings, we used the term "biochemical genetic screening," to talk about screening for heritable traits. In that case, it is not induced damage, but it is inherited traits that might cause a worker to be predisposed to illness.

Mr. GORE. Where does biochemical screening fit into your two categories, or is it a third category?

Mr. KARNY. We thought it was confusing and we decided to drop that and change the terminology a little bit from the last hearing.

Mr. GORE. So now it is in with noncytogenetic screening?

Mr. KARNY. It is really in the genetic screening. What we called in the last hearing "biochemical genetic screening" is what we are now calling "genetic screening." On the other hand, the monitoring techniques look for the damaged chromosomes, or DNA, and only as a way to distinguish another small group of tests, we used the term "noncytogenetic."

Mr. GORE. You have two categories, and one of the two categories has two subcategories, genetic screening, which is what we were calling "biochemical genetic screening," and genetic monitoring, with two subcategories, cytogenetic monitoring, which essentially looks for chromosome damage and infers from the damage the probability that there is a causative agent in the nearby environment?

Mr. KARNY. That is correct.

Mr. GORE. Noncytogenetic monitoring, which seeks to accomplish the same goal by——

Mr. KARNY. It is a finer kind of test. It looks to damage to the DNA itself.

Mr. GORE. It looks for damage to the DNA rather than to the chromosomes?

Mr. KARNY. Yes. These are at the experimental level, and I do not propose to really say much more about them today. We will

concentrate on the genetic screening and cytogenetic monitoring. Those are the major techniques.

Mr. SHAMANSKY. Mr. Chairman, let me display my lack of understanding here.

Mr. GORE. Now that I have, go ahead.

Mr. SHAMANSKY. For the purposes of our discussion today for definition, contrast cytogenetic from noncytogenetic in this layman's terms. I understand genetic, but the subcategories of cytogenetic as distinguished from noncytogenetic——

Mr. KARNY. Both cytogenetic and noncytogenetic techniques look for damage to the genetic material as a result of exposure to some hazardous agent or substance such as ionizing radiation or a chemical. The term "cytogenetic" applies to the chromosomes in the cell. These are structures which are visible with appropriate techniques under a microscope, and these are the large structures that carry the individual genes, thousands of individual genes. You cannot see the genes on the structures, but you can, with cytogenetic techniques, see aberrations in the large structures, which may cause problems.

The actual genes themselves are composed of DNA. That chemical can be examined by various laboratory techniques, and those techniques are what we put under the rubric of noncytogenetic. That is a finer technique that looks for the damage to the actual gene itself. The DNA molecule might be broken or otherwise damaged from some of these environmental insults.

Mr. SHAMANSKY. You are using the expression "methods" so a cytogenetic method would be what, a microscope looking at a chromosome?

Mr. KARNY. Essentially. I could ask Dr. Newell to elaborate on the scientific procedure.

Mr. SHAMANSKY. I am a lawyer dealing with science, so you have to make this transition. "Noncytogenetic method" refers to something other than a regular microscope?

Mr. KARNY. That is correct.

Mr. SHAMANSKY. Like an electron microscope——

Mr. KARNY. Chemical methods.

Mr. SHAMANSKY. We are distinguishing looking through a microscope as using chemicals to tell us something?

Mr. KARNY. Yes, in this category.

Mr. SHAMANSKY. Thank you very much. It is a matter of definition.

Mr. KARNY. With respect to cytogenetic techniques the actual detection of their chromosome damage is a fairly complex procedure, but if the laboratory variables are kept constant, chromosome damage can be detected reliably.

A large number of epidemiological studies using cytogenetic techniques have been done on workplace populations. Those studies were directed to testing the correlation between the chromosome damage and increased risk of disease. However, several factors complicate interpretations of those studies. In very few cases has the level of exposure of the workers to the hazard been documented, making establishment of a dose-response relationship impossible. Other factors such as age, smoking, drinking habits, nutrition-

al status, and the presence of disease can cause differences in the level of chromosome damage, also.

Studies done on populations exposed to ionizing radiation, including atomic bomb survivors in Japan, are less equivocal than those done on chemical exposure, mainly because exposure levels to ionizing radiation are more easily documented. The evidence from those studies shows an increase in chromosome damage with an increasing dose of radiation. The studies on these survivors have shown these clear dose-related increases in aberrations and in various cancers for the populations as a whole. However, there seems to be no correlation between high frequencies of chromosomal aberrations or damage, if you will, and the risk of cancer for individuals.

From the published studies in this field, therefore, it is not possible to tell if cytogenetic monitoring can be used to set safe exposure levels in the workplace. Neither is it clear that cytogenetic monitoring will prove to be an indicator of risk for disease either for populations or for individuals. Because good epidemiological studies are being organized and because some of the studies done to date have shown some evidence to suggest that chemicals cause genetic damage, research exploring and perfecting these techniques is warranted.

With respect to genetic screening, that technique is based on the fact that the human species is biologically diverse. Therefore differential susceptibility to chemicals is likely. In fact, differential reactions to drugs on the basis of genetic makeup have been documented. Explicitly defining this susceptibility, however, is not possible given our current state of knowledge.

We found that most of the tests for identifying the traits are reliable, valid, and have a high specificity and sensitivity for the trait. However, there are few data to support the correlation between any of these traits and an increased risk for diseases from occupational exposures, mainly because of serious flaws in study designs. The epidemiological studies that have been done do offer suggestive evidence, though, for the correlation of certain traits and particular diseases.

At this point I would like to move on to our findings with respect to legal issues.

This technology raises a number of legal issues related to workplace safety and employee rights. Although the law has generally not dealt with this topic, many existing legal principles are directly applicable to the issues raised. Moreover, employers and unions could negotiate mutually agreeable solutions to the problems raised by genetic testing.

Under our laws, the employer has the responsibility for workplace safety. Failure to meet that responsibility can result in costly judgments or in civil or criminal penalties against the employer. For example, if genetic screening were highly predictive of future illness, the employer would likely be negligent if it ignored the results of screening and placed the employee in a high-risk environment.

Under the Occupational Safety and Health Act of 1970, the Secretary of Labor can promulgate standards to protect all employees from toxic substances. However, those standards must be directed

toward a significant risk of material health impairment, and they must be technologically and economically feasible. The feasibility requirement may leave some percentage of workers at risk. Of those workers at risk, some may be genetically susceptible and others may be at increased risk because of genetic damage. Whether a standard could protect a small number of individuals or whether it would fail to meet the significant-risk test because of that small number is currently an unresolved question.

The Occupational Safety and Health Act and its regulations neither prohibit nor require genetic testing. However, the Secretary of Labor has broad authority to regulate employer medical procedures as long as the regulation is related to worker health and meets those prior requirements that I mentioned. Therefore, the Secretary could require genetic testing in its various forms if the techniques were shown to be reliable and reasonably predictive of future illness. The Secretary could also regulate the use of genetic testing, but only to the extent that the regulation was related to worker health. The act grants no authority over rights and conditions of employment per se and no authority to protect applicants for employment from discrimination.

In cases of employment discrimination on the basis of genetic makeup, Federal and State antidiscrimination statutes may offer some relief. Title VII of the Civil Rights Act of 1964 prohibits discrimination in employment based on race, color, religion, sex, or national origin. In addition to intentionally discriminatory actions, neutral employment practices that have a disparate impact on the protected group may violate title VII. Some genetic screening, such as for sickle cell trait, would have a disparate impact. Therefore, a black employee would have a prima facie case of discrimination against the employer. Then the employer would have the burden of justifying the screening program by demonstrating its relation to legitimate job requirements or business needs. It is presently unclear whether avoiding tort liability or costly engineering controls is a business necessity or whether the employee's capacity to perform the job without risk of future illness is a job-related characteristic. However, it is clear that any job selection method must be predictive of the characteristic for which it allegedly selects. Since genetic screening is currently of low or uncertain predictive value, a program that had a disparate impact on the employment opportunities of the classes protected by title VII would violate that act.

The Rehabilitation Act of 1973 prohibits employment discrimination against otherwise qualified handicapped people by employers who are Government contractors or recipients of Federal assistance. Virtually all the States have similar statutes, and State laws usually offer broader protection to handicapped people. These statutes offer a greater potential than title VII for aiding the employment opportunities of genetically susceptible individuals. However, for those laws to be applicable two currently unresolved legal questions must be settled in favor of the employees. The first is whether or not genetic makeup is a handicap. If not, these employees would obviously have no rights under that statute. If it is a handicap, the next question is whether employment may be denied to handicapped individuals on the basis of probability of future illness. If the courts were to rule that risk of future illness was not a

legitimate area of inquiry for employers, the Rehabilitation Act and similar statutes would prohibit adverse job actions on the basis of genetic traits. If risk of illness were recognized as a legitimate matter of concern, the employer would have the burden still of showing that the genetic screening techniques were reasonably predictive of illness. Finally, even if the employer could show that the tests were predictive, there may have to be an accommodation to these genetically handicapped employees. Such accommodation however would not require the installation of expensive engineering controls.

At this point I would like to move on to the ethical considerations and touch on this very briefly, since others will be covering this in detail.

In the absence of direct legal precedents and widespread experience with genetic testing, it is appropriate to consider ethical principles. However, these general principles often conflict in their application to specific situations, and that is the case with genetic testing.

Genetic screening and monitoring are not inherently unethical. Whether or not they are consistent with ethical principles will depend upon how the tests are done and how the information is used.

Ethical principles constrain how the results of genetic testing may be used. With a low correlation between genetic end points and disease it would be unethical for the employer to act adversely to the employee's interests such as by denying him or her a job. However, in the hypothetical case of a high correlation between genetic endpoints and disease, the morally correct course of action is significantly less clear. For example, the principle of beneficence, that is, do good, might be used to justify excluding these workers from a harmful situation. On the other hand, there is a countervailing principle of autonomy which says that workers should make that choice themselves. For that reason, an employer may permit or may be justified in allowing the genetically susceptible individual to assume these risks on the basis of informed consent. Finally, whether or not genetically susceptible people are entitled to compensation depends upon which of several competing theories of justice is chosen.

Finally, with respect to an economic evaluation of genetic testing, we examined the possibility of using cost-benefit and cost-effectiveness analysis to assess this technology. However, a rigorous economic analysis was not possible because of the lack of knowledge about the predictive value of the tests, the numbers of people to whom testing could be applied, and the amount of occupational disease that could be prevented.

In conclusion, I would like to emphasize that genetic testing in the workplace is an emerging technology. Although only a handful of companies are using it now, many more are interested. Its ability to predict individuals or groups that may be at increased risk of occupational illness has not been demonstrated, but there is a theoretical basis and some evidence for believing such predictions may someday be possible.

Although genetic testing has the potential to play a role in the prevention of occupational disease, it also has the potential for

misuse. Current law provides some incentives for its use and some safeguards against its misuse. Established ethical principles provide some guidance for its use. However, there are many questions that remain unresolved.

At this time I would be happy to answer any of your questions.

[The prepared statement of Mr. Karny follows:]

11-575- 0 - 83 - 2

STATEMENT OF

GEOFFREY M. KARNY, PROJECT DIRECTOR

BIOLOGICAL APPLICATIONS PROGRAM

OFFICE OF TECHNOLOGY ASSESSMENT

CONGRESS OF THE UNITED STATES

BEFORE THE

SUBCOMMITTEE ON INVESTIGATIONS AND OVERSIGHT

COMMITTEE ON SCIENCE AND TECHNOLOGY

UNITED STATES HOUSE OF REPRESENTATIVES

ON

THE ROLE OF GENETIC TESTING IN THE PREVENTION OF OCCUPATIONAL ILLNESS

OCTOBER 6, 1982

Mr. Chairman and Members of the Subcommittee:

I am pleased to appear here today on behalf of the Office of Technology Assessment (OTA) to present the preliminary findings of OTA's assessment of The Role of Genetic Testing in the Prevention of Occupational Illness. I am the project's director, and with me is Dr. Nanette Newell, a geneticist who was responsible for the scientific part of the study. The study was undertaken last October at the request of the House Committee on Science and Technology and this Subcommittee. Although it is near completion, our draft report must undergo additional review by outside experts and has not yet been presented to the Technology Assessment Board. Therefore, these findings should be considered preliminary and not the official findings of OTA.

The Use of Genetic Testing for the Prevention of Occupational Illness

The term genetic testing applies to several techniques used to examine workers for particular inherited genetic traits or environmentally induced changes in their genetic material on the assumption that the traits or changes may predispose them to illness. There are two inherently different kinds of testing, genetic monitoring and genetic screening, whose results can be used in the workplace for very different purposes.

Genetic monitoring involves periodically examining a group of workers by collecting blood or other body fluids to assess whether genetic damage has occurred in certain cells. This damage may indicate exposure to a hazardous agent, such as a carcinogenic chemical or ionizing radiation. It may also indicate the possibility that the exposed group will be at an increased risk of developing disease, most likely cancer. The ability of the tests to predict disease, if demonstrated, would apply only for the exposed group as a whole; there is no way yet to identify which individuals in the group who are

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at increased risk. If the scientific validity of genetic monitoring were established, it would have potential as an early warning system, by indicating that exposures to known or suspected carcinogens are too high or that a previously unsuspected chemical should be viewed as a potential carcinogen.

In contrast, genetic screening is a one time testing procedure to determine if a person has particular genetic traits, regardless of whether the person has been exposed to a hazardous substance. The traits are identified through laboratory tests on body fluids, usually blood. Some scientists have hypothesized that these genetic traits might predispose an individual to adverse health effects in the presence of particular chemicals. While normally not harmful, the traits theoretically may make the individual more susceptible to blood-damaging chemicals, pulmonary irritants, oxygen deprivation, or other physical or chemical stresses in the workplace.

In sum, screening has the potential to determine individual susceptibility, whereas monitoring may be able to assess a chemical's effect on an exposed population in order to determine if that population is at increased risk. Because of this distinction, screening can be used to exclude genetically susceptible individuals from jobs where they would be exposed to hazardous substances, whereas monitoring would most likely indicate a need to lower exposure levels for a group identified to be at increased risk.

Although this technology is still in its infancy, its advocates believe that it might be able to play an important role in the prevention of occupational disease. It is technologically and economically impossible to attain a no-risk workplace by lowering the level of exposure to hazardous substances to zero. However, if individuals or groups who were predisposed to occupational illness because of past or potential exposure to hazardous

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substances could be identified, other preventive measures could be taken by the company or the workers themselves. In addition to the obvious and significant benefits from preventing serious illnesses, there could be indirect benefits, such as a reduction in the costs associated with occupational illness for employers, employees, and society. These costs include medical, insurance, and legal expenses, time lost from work, and disability or unemployment payments.

The use of this emerging technology, however, raises several questions. Are the techniques sufficiently developed so as to predict reliably an association between either genetic damage or a person's genetic makeup and disease? How much of the variation in risk can be attributed to such predisposing genetic factors and how much to variation in environmental exposure? Since many of the genetic traits sought in screening happen to be distributed unevenly among some races and ethnic groups, could the use of the tests result in discrimination on the basis of race, sex, or national origin? How will the availability of the tests affect the employer's responsibility for maintaining a safe workplace? How might these procedures affect efforts to reduce the level of hazardous substances in the workplace? If the tests are predictive, then to what degree should society protect high risk individuals or groups, at what cost, and who should bear that cost?

Although it is too soon to be able to answer many of the troubling questions raised by genetic testing, it is not too soon for society to begin to think about them. As we reported to you at your June 22nd hearing, our survey of major companies and unions found considerable interest in the potential of genetic testing.

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Because genetic testing in the workplace is an emerging technology, there is insufficient evidence to assess many of its potential benefits, risks, and impacts. However, we did examine the degree to which it has been used, the current stage of its development, expected future developments, and the various legal, ethical, economic, and policy issues that it raises. Since there have been no significant changes in our findings on the actual use of genetic testing that we presented to you at the hearing on June 22, 1982, the remainder of this statement will concentrate on our preliminary findings on the scientific and social issues.

State of the Art

Our assessment of the state of the art required a two-stage approach. First, we evaluated the reliability and validity of the laboratory tests themselves. Then we evaluated existing data on the correlation between the genetic damage or trait in question and an increased risk for disease. Our conclusion is that none of the current genetic tests meet established scientific criteria for routine use in an occupational setting. However, there is enough suggestive evidence to merit further research.

Genetic Monitoring

The concept of monitoring workplace populations for genetic damage from chemicals or ionizing radiation is well grounded on a theoretical and experimental base. Ionizing radiation and a wide range of chemicals can cause damage to the genetic material in experimental animals and, in some cases, humans. This damage may result in mutations, which are changes in the genetic information. The consequences of increasing the mutation rate in somatic cells of a population are not well understood, but mutations have been implicated in several diseases, most importantly cancer.

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There are two major types of genetic monitoring methods -- the older, established cytogenetic methods, which detect major structural changes in chromosomes and the newer noncytogenetic methods, which detect actual DNA damage. The noncytogenetic methods, for the most part, are still in experimental stages, but could eventually lead to faster and less expensive monitoring methods.

The actual detection of chromosome damage using cytogenetic techniques is a fairly complex procedure. It requires skilled laboratory technicians and is often labor intensive. But if laboratory variables are kept constant, chromosome damage can be reliably determined.

A large number of epidemiological studies using cytogenetic techniques have been done on workplace populations, but there are several factors that make the interpretation of these studies difficult. In very few cases has the level of exposure of the workers to the hazard been documented, making the establishment of a dose-response relationship impossible. Also, it is fairly well established that other factors such as age, smoking and drinking habits, nutritional status, and the presence of disease can cause differences in the level of chromosome damage. Because most studies have not taken these factors into account, interpretations of these studies are difficult. Finally, it is not known whether chromosomal changes in blood cells reflect the presence of chromosome damage in internal organs.

Studies done on populations exposed to ionizing radiation, including atomic bomb survivors in Japan, are less equivocal than those done on chemical exposure, mainly because exposure levels to ionizing radiation are more easily documented. The evidence does show an increase in chromosome damage with increasing dose of radiation. This damage, though, has not been correlated

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with an increased risk for disease with one exception. Extensive studies on the bomb survivors have shown clear dose-related increases in chromosome aberrations and in various cancers for these populations as a whole. However, there seems to be no correlation between high frequencies of chromosome aberrations and risk for cancer for individuals.

From the published studies in this field, it is not possible to tell if cytogenetic monitoring can be used to set safe exposure levels in the workplace. Neither is it clear if cytogenetic monitoring will prove to be an indicator of risk for disease, either for populations or for individuals. Because good epidemiological studies are being organized and because some of the studies done to date have shown some evidence to suggest that chemicals cause genetic damage, research exploring and perfecting these tests is warranted.

Genetic Screening

It is well known that the human species is biologically diverse; therefore, differential susceptibility to chemicals is likely. In fact, differential reaction to drugs on the basis of genetic makeup has been documented. Explicitly defining this genetic differential susceptibility, though, is not possible given the current state of knowledge. The few genetic traits covered in this assessment were chosen because some data exist which implicate them in susceptibility differences to certain chemicals. The list probably represents only a small percentage of the genetic traits involved in responses to chemicals. We studied the following traits: glucose-6-phosphate dehydrogenase deficiency, sickle cell trait, alpha and beta thalassemia trait, NADH dehydrogenase deficiency, serum alpha$_1$-antitrypsin deficiency, aryl hydrocarbon hydroxylase inducibility, slow versus fast acetylation, human

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leukocyte antigens, carbon oxidation, diseases of DNA repair, and several other less well characterized genetic traits.

We found that most of the tests for identifying the traits are reliable, valid, and have a high specificity and sensitivity for the trait. However, there are few data to support the correlation between any of these traits and an increased risk for diseases from occupational exposures, mainly because of serious flaws in study designs. The epidemiological studies that have been done do offer suggestive evidence, though, for the correlation of certain traits and particular diseases.

Genetic Testing and the Law

Genetic testing raises legal questions related to workplace safety and employee rights. Although the law has generally not dealt with genetic testing, many existing legal principles are directly applicable to the issues raised by this technology. Moreover, employers and unions could negotiate mutually agreeable solutions to the problems raised by genetic testing. Unions, however, have no legal duty to bargain over such issues or to take special steps to protect workers who might be at increased risk.

Under our laws, the employer has the responsibility for workplace safety. Failure to meet the responsibility can result in costly judgments or civil or criminal penalties against the employer. Thus, if genetic screening were highly predictive of future illness, the employer would likely be negligent if it ignored the results of screening and placed the employee in a high-risk rather a than low-risk environment. However, recovery of damages by an employee who developed the predicted illness would probably be barred by the "exclusive remedy" provision of workers' compensation laws and possibly by the doctrine of assumption of the risk, if the employee had been informed of

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the risk. If the risk had been concealed from the employee, recovery would probably not be barred under workers' compensation laws, and the employer would face the possibility of punitive damages.

Under the Occupational Safety and Health Act of 1970 (OSH Act), the Secretary of Labor is empowered to promulgate standards that protect all employees from toxic substances to the extent that the standards are directed toward a significant risk of material health impairment and to the extent that they are technologically and economically feasible. These standards can, among other things, set maximum exposure levels, require personal protection gear, and mandate various medical procedures. The feasibility requirement may leave some percentage of exposed workers at risk, depending on the circumstances of the particular hazardous substance and industry. Of those workers at risk, some may be genetically susceptible and others may be at increased risk because of genetic damage. Whether a standard could protect a very small number of susceptible individuals or whether it would fail to meet the significant risk test because of the small number of workers involved is an open question.

The OSH Act and regulations thereunder neither prohibit nor require genetic testing. However, the Secretary of Labor has broad authority to regulate employer medical procedures as long as the regulation is related to worker health and meets the significant risk and feasibility requirements. Therefore, the Secretary could require genetic testing in its various forms, if the techniques were shown to be reliable and reasonably predictive of future illness. The Secretary also could regulate the use of genetic testing, but only to the extent that the regulation was related to employee health. The Act grants no authority over rights or conditions of employement per se and no authority to protect applicants for employment from discrimination.

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For those applicants or employees who were subject to some adverse job action because of their genetic makeup, Federal and State anti-discrimination statutes may offer some relief. However, they do not deal specifically with genetic screening except for a few state statutes that prohibit employment discrimination on the basis of certain genetic traits, usually sickle cell trait.

Title VII of the Civil Rights Act of 1964 prohibits discrimination in employment based on race, color, religion, sex, or national origin. In addition to intentionally discriminatory actions, neutral employment practices that have a disparate impact on a protected group may violate Title VII. Some types of genetic screening, such as for sickle cell trait, would have a disparate impact; therefore, an adversely affected genetically susceptible employee in one of those classes would have a prima facie case of discrimination against the employer. Then, the employer would have the burden of justifying the screening program by demonstrating its relation to legitimate job requirements or business needs. It is presently unclear whether avoiding tort liability or the cost of engineering controls is a business necessity or whether the employee's capacity to perform the job without a risk of future illness is a job-related characteristic. However, it is clear that any job selection method must be predictive of the characteristic for which it allegedly selects. Since genetic screening is currently of low or uncertain predictive value, a program that had a disparate impact on the employment opportunities of the classes protected by Title VII would violate that Act.

The Rehabilitation Act of 1973 prohibits employment discrimination against otherwise qualified handicapped people by employers who are government

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contractors or recipients of federal assistance. Virtually all of the states have similar statutes, and the state laws usually offer broader protection to handicapped people. These statutes offer a greater potential than Title VII for aiding the employment opportunities of genetically susceptible individuals; however, for those laws to be applicable, two currently unresolved legal questions must be settled in favor of the employees. The first is whether or not genetic makeup is a handicap. If not, these employees would have no rights under these laws. If it is a handicap, the next question is whether employment may be denied to handicapped individuals on the basis of a reasonable probability of future illness. If the courts were to rule that future risk of illness was not a legitimate area of inquiry for employers, the Rehabilitation Act and similar statutes would prohibit adverse job actions on the basis of genetic constitution. If risk of illness were recognized as a legitimate concern, the employer would have the burden of showing the genetic screening techniques were reasonably predictive of illness. Even if the employer demonstrated this, however, it might have to accommodate the "genetically handicapped" employee anyway. But such accommodation would not require the installation of expensive engineering controls.

The Ethics of Genetic Testing

In the absence of direct legal precedents and wide-spread experience with genetic testing, it is appropriate for policy-makers to consider ethical principles. Ethics may be defined as the study of moral principles governing human action. These principles, or general prescriptive judgments, create moral duties that guide action in particular circumstances. Sometimes, however, the principles conflict in their application and provide no clear guidance. Then, difficult choices must be made. This is the case with genetic testing in the workplace.

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Genetic screening and monitoring are not inherently unethical. Whether or not they are consistent with ethical principles will depend on how the tests are done and how the information is used.

Ethical principles regarding the duties of company medical personnel toward workers are often conflicting or not well established. Therefore, they offer little specific guidance about the manner in which tests should be conducted with the exception of procedures done for purposes of medical research. In case of research on humans, ethical principles are well-established and provide for the rigorous protection of individual rights and interests.

Ethical principles constrain how the results of genetic testing may be used. With a low correlation between genetic endpoints and disease, it would be unethical for the employer to act adversely to the employee's interests, such as by denying him or her a job. In the hypothetical case of a high correlation between genetic endpoints and disease, the morally correct course of action is significantly less clear. An employer may be justified in allowing a genetically susceptible person to assume the risks on the basis of informed consent. On the other hand, the most ethically feasible course of action for an employer once genetic monitoring identifies a high risk group would be to reduce worker exposure. Failure to do so would be inflicting harm, and it is unlikely that the group would consent to assuming this risk. Finally, whether or not genetically susceptible people are entitled to compensation depends on which of several competing theories of justice is chosen.

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Economic Evaluation of Genetic Testing

Genetic testing in the workplace has potential benefits and costs to workers, employers, and society as a whole. The magnitude and distribution among the sectors of society of these benefits and costs will help determine the desirability of this approach to improving occupational health. Two techniques of economic evaluation -- cost benefit and cost-effectiveness analysis -- are methods for collecting, organizing, and presenting evidence about the benefits and costs of alternative courses of action so that choices can be made. They are systematic approaches to examining the trade-offs among the different kinds of consequences -- for example, dollar outlays today versus improved levels of health five years hence -- stemming from a decision.

The usefulness of economic evaluation rests on its ability to improve decisions. Even when economic analysis is severely limited by uncertainties about the magnitude, direction, or value of certain consequences, as with genetic testing, it can still be a useful exercise. The very identification of key areas of uncertainty, for example, can be used to set priorities for further research. Thus, economic evaluation can be used to dissect and examine alternative strategies in order to understand their underlying assumptions and uncertainties.

In the case of genetic testing, rigorous economic analysis of the costs and benefits is not possible because of the lack of knowledge about the predictive value of the tests, the numbers of people to whom testing could be applied, and the amount of occupational disease that could be prevented. However, economic analysis could provide a rough sense of the benefits, burdens, and trade-offs associated with genetic testing programs.

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Conclusion

Genetic testing in the workplace is an emerging technology. Although only a handful of companies are using it now, many more are interested in it. Its ability to predict individuals or groups that may be at an increased risk of occupational illness has not been demonstrated, but there is a theoretical basis and some evidence for believing such predictions may some day be possible.

Although genetic testing has the potential to play a role in the prevention of occupational disease, it also has the potential for misuse. Current law provides some incentive for its use and some safeguards against its misuse. Established ethical principles also provide some guidance for its use. However, there are many questions that remain unresolved.

At this time, I would be happy to answer any of your questions.

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Mr. GORE. Thank you very much for an excellent statement, and again thank you for the excellent work you have been doing over there. I found it very interesting in your statement.

Early on you said that you do not think the tests currently in use are sufficiently accurate or predictive to justify their use; is that correct?

Mr. KARNY. They do not meet established scientific criteria for their routine use to predict risk of illness; that is correct.

Mr. GORE. When you talk about how predictive a test is, correct me if I am wrong here, but my understanding of it is that there are two general guidelines that you can use. First of all, how many false positives are there? Second, how many false negatives are there? In other words, if you are using a test to predict whether or not a person is more likely to get brown lung disease and the test will have—will say that 5 out of 10 people tested have brown lung disease—whether or not they are likely to get brown lung disease, whether or not they really are more susceptible, then that test will have a large number of false positives. In other words it will predict some people will have the susceptibility who really will not. That is a false positive. If you have too many false positives, then that test is not a good one.

On the other hand, if you have a test that will tell you that somebody is not more susceptible to a given disease, when actually that person is more susceptible, then that test has identified what the scientists call a false negative. Now, if you have got a test that has a whole lot of false positives and a whole lot of false negatives, either one, the test is—it may not meet generally accepted scientific standards.

Dr. Newell, is that a rough layman's explanation of what we are talking about here?

Ms. NEWELL. Yes; the number of false positives and false negatives determines the validity of the test. The test also has to be reliable, which means that it has to give the same results on the same individual over a period of time. So when we use the terms "reliability" and "validity," that is what we are referring to.

Mr. GORE. Now, there are a lot of tests that are currently in use in society that have a good number of false negatives and false positives. For example, a polygraph or a lie detector test has a certain number of false negatives that we would know it will predict and a certain number of false positives, yet the number is low enough that some courts will accept it, will they not?

Mr. SHAMANSKY. I do not know about some courts. This lawyer would not let his client use it, because it is just not reliable, in my opinion.

Mr. GORE. Well, in fact it is used by employers now to help guard against theft by employees. There are all kinds of scientific tests that have a certain number of false negatives and false positives. Now, what you are saying here, one of the things that you are saying in your testimony is that the genetic screening tests that are now available and that some are using have so many false positives and false negatives that the people using them are probably not justified in using them because the person who is an object of a test is sort of playing roulette or—is that——

Mr. KARNY. We are saying that the tests are not of the nature that they can really reasonably predict the risk of future illness. Now, if they are being used for that purpose, in an attempt to predict risk of future illness, the data do not support any reasonable correlation there. Now, that does not say anything about research on the tests to determine exactly how predictive they might be or learn something more about the underlying disease mechanisms and so forth. But as to predicting future illness, the evidence does not demonstrate that predictive nature.

Mr. GORE. How long do you think it will be before such tests are predictive and more accurate? They are making a good deal of progress, are they not?

Ms. NEWELL. Let me answer that question. First of all, let us take some genetic screening tests, for instance sickle cell. That test is very reliable and very valid. The problem is that once you have a set of people who have sickle cell trait, then what you cannot do is predict their risk for disease in the presence of harmful chemicals. If you were to do a good cross-sectional epidemiological study on people who had sickle cell trait, or some of the other deficiencies we have been studying, and follow those people in industrial settings using appropriate controls, it is possible that you could come up with an idea of their risk for disease from certain types of chemicals within a couple of years. On the other hand, if you are looking at the monitoring tests, the tests themselves are not sufficiently reliable or valid yet. The actual laboratory methodology is not well established. Also, those tests which detect genetic damage are most likely determining susceptibility to cancer, and since the latent period between exposure and the development of the disease is so long, a good epidemiological study to determine the risk for disease would take a very long time.

Mr. GORE. All right. So we have really got two sets of issues. There are a whole range of issues that we will have to deal with soon when the tests become sufficiently accurate and predictive, and that will probably take place within what, 2 to 10 years, is that a fair range of estimate?

Ms. NEWELL. Yes.

Mr. GORE. But right now, even while the tests are not reasonably predictive, there are pressures that employers feel to use them anyway, just as we had testimony from a railroad attorney who said that they now use a technique that is not really genetic screening, but they will X-ray the backs of people applying for jobs to look for a curvature of the spine, because they have a prevalence of back injuries in railroad employment, people jumping off moving cars; yet the X-ray of that person's back is not very predictive of whether or not that person is going to get a back injury later on. It is not reasonably predictive, but they make job applicants go through that anyway. Why? Because even if a very tiny predictive test—even a very tiny result is legally useful, or at least their lawyers tell them that they need to do that.

Some of the genetic screening techniques are in the same category. They are not very predictive, but there are legal pressures on companies to use them anyway, and that poses another set of issues: How can job applicants and employees be protected from the use of techniques that are just not reasonable scientifically?

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You are saying in your testimony that there are laws currently on the books that with some amendment or modification could probably do this job; is that correct, Mr. Karny?

Mr. KARNY. Yes. Let me elaborate on that.

Mr. GORE. All right.

Mr. KARNY. The law grows in a sense through case decisions. You have statutes and then you have court cases interpreting those statutes. There are statutes and established court cases which could evolve in the direction of protecting this kind of individual, particularly under the Rehabilitation Act. There are a number of State court cases and there is one Federal case—they vary. They are all over the lot, but I could see the situation where the law would evolve to find such a person to be handicapped and then look at the basis upon which they were excluded from employment to see whether or not that was predictive, and if it were not predictive, then to find that, for example, the Rehabilitation Act or the State equivalent would apply and prohibit the discrimination.

Mr. GORE. Where on the spectrum of predictive values would you draw the line of reasonableness, if it is 5-percent predictive, 90-percent predictive—presumably it would be neither of those extremes.

Mr. KARNY. You want to answer that question?

Ms. NEWELL. In a hospital setting, when you are testing for genetic traits, you usually try and have your test be 95-percent accurate.

Mr. GORE. Ninety-five-percent accurate.

Ms. NEWELL. That is not predictive for the disease, that is accurate for determining false positives or false negatives.

Mr. GORE. I see. We had testimony earlier from an attorney for one of the largest railroads in this country that if a test was predictive of a 5-percent greater susceptibility, the attorney would advise his client to deny employment. So we have got quite a range there. If at least one major corporation in the country sees a 5-percent elevated probability of susceptibility as justifying job exclusion, and yet the medical community typically uses a 95-percent figure, then there is a wide range. Am I using apples and oranges here?

Mr. KARNY. The testimony given by the railroad lawyer indicates that he did mix up some terms. There is a difference between the predictive value of the test and the increased risk. A test that is 5-percent predictive is a pretty low value test. In other words——

Mr. GORE. Yes.

Mr. KARNY. It may catch 5 of the 100 cases that it should. Now, that is different from a 100-percent predictive test that defines somebody with a 5-percent increase in risk, and you have to keep those two concepts straight.

Also on the concept of increase in risk, a 5-percent increase in risk is pretty minimal, as I understand it. Generally, in epidemiological studies you look for perhaps a doubling in risk or even more.

But to go back to your first question, I think in terms of what is the acceptable predictive value of a test, it depends on a lot of circumstances. I am not an expert in the scientific aspects of genetic screening, but from what I know about it, they use tests of lower predictive values for screening newborns and accept some false positives and some false negatives, because they have found through

an analysis of the cost-effectiveness of the program that it is useful for preventing disease. So I do not think we are looking for a 90- or 95-percent predictive value on a test. The courts say the tests should be reasonably predictive, but they really have not elaborated on that point.

Mr. GORE. OK. I have this testimony here and I asked him about the X-ray use and I asked would you advise legally the denial of employment to someone who had a 5-percent predictive X-ray or other indicator? And he said yes, my advise would be yes. I asked, what about a 1 percent? He said that would be de minimus. I asked 2 percent. He said he did not know, but he thought that somewhere between 2 percent and 5 percent would be the cutoff line.

Now, he may have been mixing up—I may have been mixing up predictive value and higher susceptibility.

Mr. KARNY. I can understand the point being made there in terms of advising the client not to take a chance. But that is not necessarily required by law. He is advising his client of his view on how to avoid legal liability. I think the courts would find a 5-percent predictive test to be very troublesome.

For example, there was a State case, I believe in Wisconsin, involving an epileptic, where there was something like a 10- or 20-percent chance that this person would have seizures on the job. And that raises questions of safety, too, which are often not involved here. The court found a 10- to 20-percent chance to be "a mere possibility", which was not sufficient to deny the person the job under the State antidiscrimination statute.

Mr. GORE. Let me ask you a couple more quick questions, and then I want to call on Mr. Shamansky.

First of all, you have testified that a person who is denied a job because of his or her genetic makeup might well be classified as a handicapped person within the meaning of the Rehabilitation Act, and as such might have a legal claim against the person who denied him or her a job on the grounds of genetic makeup; is that correct?

Mr. KARNY. Yes.

Mr. GORE. No such cases have been resolved to date, have they?

Mr. KARNY. That is correct. Under the Rehabilitation Act.

Mr. GORE. Now, could an employer be caught in a whipsaw where he would be liable for not—he would be liable if he went ahead and gave a person with increased susceptibility a job and that person later contracted an occupational disease, yet on the other hand he might be liable under the Rehabilitation Act if he refused a job? Is that possible?

Mr. KARNY. I think it is possible. It needs consideration. Some of the philosophy behind the Rehabilitation Act encompasses the idea that handicapped people have a right to try and a right to fail. Now, whether that provides a right to get sick is an open question. I do not know the answer. We are just beginning to deal with that question.

I think there is another consideration to bear in mind. Workers' compensation laws are designed to take care of occupational illness. And there is a bar generally against suits by employees against employers because the exclusive remedy for the employee is to file a claim under the workers' compensation law. It is a form

of insurance. So the employer would generally be protected to that extent.

Now, again, somebody would have to pay the cost of that illness. Let us assume that a test is reasonably predictive. Somebody is going to have to bear the cost of that illness. Initially, the employer and its insurance company will bear the cost, but eventually society will. But that is a balancing question that society has to make decisions on and perhaps Congress needs to consider.

Mr. GORE. Now, if an employer had a genetic screening test that showed a higher than average susceptibility for a specific job applicant, and that job applicant was hired and went on the job, contracted the occupational disease, and then recovered under workmen's comp, if he had not been made aware—if the employee had not been made aware of the results of that genetic screening, then he might also be able to sue the employer directly on grounds that the information had not been made available to the employee; is that correct?

Mr. KARNY. That is correct.

Mr. GORE. So here we have a legal standard that should serve to insure that employees subjected to genetic screening tests are made aware of the results of those tests, should it not? It would seem to me that employers ought to react that way if the failure to disclose would remove the bar to suits by employees collecting under workmen's comp.

Mr. KARNY. I do not know that I want to make a judgment on what employers ought to do in terms of the way you structured the question and in terms of the legal environment. It would be probably in their best interest to disclose the results of the test to the employee.

I think under that circumstance, I would advise the employer, if I were their counsel, to disclose those results.

Mr. GORE. Business lawyers in this country, after your analysis of this subject, you would think that if they are doing their job, they ought to be advising any clients using genetic screening tests to make the results available to their employees and have an open information policy.

Mr. KARNY. I would say only under the hypothetical situation of the tests being highly predictive.

That is the clearer situation.

For a test of low predictive value, I think that is a fairly difficult question. I think the law is fairly uncertain on that question.

Ethical principles might be considered, but from the legal perspective, it is fairly uncertain as to what the employer should do.

Mr. GORE. All right. Thank you very much.

Mr. Shamansky.

Mr. SHAMANSKY. Mr. Karny, I am delighted to have a fellow lawyer around.

All these other people don't understand, you see.

On page 7 of your testimony, I think you have the paragraph beginning at the bottom of the page; I think you characterize the dilemmas fairly well, and it seems to me that we, as lawyers, are going to protect our clients as the predictability and the validity of these tests come along.

As long as the tests are not reasonably or very accurate, you cannot single out the employer for being negligent toward his obligation toward his employee, correct?

Mr. KARNY. You mean if he places a person in a higher risk environment?

Mr. SHAMANSKY. Yes.

Mr. KARNY. I would say that is accurate. If the employer did not know that he was placing a particular employee in a so-called high-risk environment, then there is no negligence.

Mr. SHAMANSKY. The minute you develop the technology that you could inform this person that this person was subject to this illness in the workplace, then he has, it seems to me, he has an obligation toward himself, and even toward the prospective employee, not to place him there?

Mr. KARNY. Probably. I don't want to be too strong because I think the standard of care would be medical practices that are accepted by the medical community and demonstrated as being valid.

Mr. SHAMANSKY. When I say technical, I meant that.

Mr. KARNY. Yes, I think the employer probably has the legal obligation to use well-established medical procedures to identify——

Mr. SHAMANSKY. Not only does he have the responsibility of using them, if he says to a prospective employee, I will not hire you because you fall outside of acceptable risk, he should not be obligated, on the one hand, by the law to hire somebody, and then be held responsible for that person's becoming ill.

Mr. KARNY. Possibly, but there are other considerations, such as the Occupational Safety and Health Act.

There is another assumption that you have to put into your hypothetical case, which is that the exposures in the workplace meet prevailing occupational safety and health standards.

Mr. SHAMANSKY. As the test becomes more predictable, the OSHA standards are affected by that very change?

Mr. KARNY. I am not sure I understand your question.

Mr. SHAMANSKY. What concerns me is that to the degree that these tests become more accurate, however—I am dealing as a layman talking to my client—if the tests can tell you that this person is a high risk, then the employer has an obligation not to subject him to, subject that employee to, that risk, although the rest of the population would not be endangered, did not have a genetic problem there.

Mr. KARNY. There are a couple of things I should elaborate upon.

First of all, risk is a continuum, and you don't have just high-risk and low-risk people. And the other point is that there are many ways to protect employees. These include engineering controls, personal protection devices being given to that employee, job rotation, or other practices; so there are a number of factors involved.

Mr. SHAMANSKY. All right. As a business lawyer, if there are a number of factors, I am going to advise my client to stay on the side of caution for his benefit, and if a prospective or present employee wants to continue the worker or expose himself to that kind of danger, how much of a right is there to get sick, and you can always say to the employee, you can always sign a waiver that you

have the risk rather than I have the risk, to the extent that the tests are predicted.

You can't force him for the norm, for the population in general, but if he falls outside the norm, then the employee, it seems to me, would have some kind of an obligation to assume the risk and not put it on the employer who says, hey, you may become ill here.

Mr. KARNY. That may be the case, but there is one other complicating factor, and that is the existence of both title VII and the Rehabilitation Act.

Mr. SHAMANSKY. What I am suggesting is, we have to reexamine those laws in the light of these things. I am assuming that the nonimmutability of these lawyers, is what I am trying to say, and the very fact that these tests are, we assume, becoming more predictable, will force us into a reexamination of the existing legislation and the commonlaw obligations under the law of tort and other things, the relationships between the employer and the employee.

Mr. KARNY. I would agree that predictive tests would force a reexamination, because they would raise the very fundamental question of who bears the cost.

Mr. SHAMANSKY. Right.

Mr. KARNY. The employee, the employer, or society—that involves a very fundamental value judgment that would have to be dealt with.

Mr. SHAMANSKY. If the employee says, well, I will waive it, then maybe he should be allowed to waive the risk, but, by the same token, you have to be sure that the employer does not force on an employee a waiver that the employee really should not have to have.

So we are getting into a very sticky wicket, based on how accurate these tests are, and it seems to me it is going to be a long time before we really know, and this is an interesting relationship, Mr. Chairman, between the law and science.

Well, thank you very much, Mr. Karny, for your testimony.

Mr. GORE. Let me ask you this: What incentives presently exist for companies to use these tests? Some are using them. Fifty-nine others have expressed an interest in using them.

Why would they use them if they are so inaccurate at the present time?

Mr. KARNY. I think they are using them for various purposes. In our survey, we found that a number were using them for research purposes. Other companies were using them routinely, and some companies were using them for a category that we defined as "Other." Few explained what they meant when they checked that box on the questionnaire.

In fact, the other category and the routine category had more responses than the research category, but I hesitate to postulate why. I might do it for one case, which is the test for sickle-cell trait.

The employers may be using the tests for sickle-cell trait routinely as part of their medical program simply to provide information to employees to make personal decisions; that is, the traditional genetic screening kinds of considerations, where people use that information to make reproductive decisions.

Mr. GORE. But there are legal pressures to cut down on the incidence of occupational disease, even though workmen's compensa-

tion laws are in effect. Still, for a variety of reasons, companies are anxious to minimize the occurrence of occupational disease?

Mr. KARNY. Absolutely.

Mr. GORE. Many companies are now identifying these techniques as a way to do that. Isn't that generally true?

Mr. KARNY. I think the companies are looking very carefully at the techniques.

We found from our survey that 17 companies had used the techniques in the past, but 6 were currently using them. Perhaps this is speculation on my part, but this drop could indicate a re-evaluation of how worthwhile the techniques are.

Mr. GORE. But 59 are considering their use within the next 5 years?

Mr. KARNY. Let me elaborate upon that 59 number.

We went back and did a further analysis of the data. The question in the survey was, are you considering the use of these tests in the next 5 years, and the answers were yes, no, and possibly.

Four of the companies said yes, and the rest said possibly; so I think what that means is they are looking carefully at genetic testing as one of a number of ways of dealing with occupational illness. They are clearly interested in research, and they would like to stay on top of the field.

I think, if I might add, these kinds of hearings, the debate in society, and the various reports on these issues certainly educate society and employers about the value of the tests, ways they could be misused, and ways to use them for acceptable purposes.

So I think employers and others who have taken a close look at these tests are evaluating them, and I think at this point hopefully a number of people see both acceptable and unacceptable ways to use them and will act accordingly.

Mr. GORE. OK. Very good.

Thank you very much, and we appreciate your testimony.

Thank you, Dr. Newell.

Our second witness is Dr. Philip Lipetz, with General Molecular Applications, Inc., from Columbus, Ohio, accompanied by John Gray, the attorney for the company.

Gentlemen, welcome to the subcommittee. You come well recommended, Doctor, and, without objection, your prepared statement will be put into the record in full at this point, and we will invite you to proceed.

Mr. LIPETZ. Thank you.

Mr. GORE. Before you proceed, I would like to welcome Congressman Bill Nelson, of Florida, a member of the full committee, who is joining us in the proceedings today.

Do you care to say anything at this point?

Mr. NELSON. Not at all.

Mr. GORE. Proceed.

[The biographical sketch of Mr. Lipetz follows:]

CURRICULUM VITAE

Philip D. Lipetz

Address 1834 Elmwood Avenue
Columbus, Ohio 43212
614-486-6924

Birthdate March 11, 1949

Birthplace Oakland, California

Marital Status Married: Linda M. Lipetz
One Child: Rebekah D. Lipetz

Education

1972 - 1978 The Ohio State University, Columbus, Ohio
Department of Biophysics
Major Areas: Molecular Genetics and Theoretical Biology
Degrees: M.S. 1976
Ph.D. 1978

1968 - 1972 Antioch College, Yellow Springs, Ohio
Major: Biology
Degree: B.A.

Employment

1982 - President of Omnimax, Inc.
(Scientific Venture Capital Co.)
Philadelphia, PA

1981 - President of General Molecular Applications, Inc.
(Biotechnology Company)
Columbus, OH

1982 - Adjunct Assistant Professor of Radiology
The Ohio State University

1980 - 1982 Assistant Professor of Radiology
The Ohio State University

1979 - 1982 Group Leader - Developmental Biochemistry Section
(14 persons)
The Ohio State University, Department of Radiology
Chemical Biological Environmental Research Group (CBERG)

1979 - 1980 Research Associate
CBERG

1978 - 1979 Research Assistant
CBERG

Research Experience

1980 - Evolutionary significance of introns - mechanisms of accelerated evolution

1980 - Alternative in vivo conformations of DNA

1979 - Measurement of DNA superstructure in aging, carcinogenic, and differentiating eucaryotes with emphasis upon gene regulation and recombination

1979 - 1981 Genetic toxicity of medical ultrasound exposure

1978 - Measurement of carcinogenic DNA damage and repair in whole animals and cell cultures; molecular prescreens for carcinogenic activity

1978 - Polyamine modulation of DNA superhelicity

1976 - 1978 Development of a model for carcinogenic promotion and possible molecular prescreen
The Ohio State University, Department of Biophysics

1975 - 1976 Photoreactivation of DNA synthesis in SHE cells.
The Ohio State University, Department of Radiology

1973 - 1974 Effect of 17-B-Estradiol on the repair of damage to DNA
The Ohio State University, Department of Radiology

1973 - 1974 Analysis of casual role of cyclobutane pyrimidine dimers in UV-induced neoplastic transformation.
Biology Division, Oak Ridge National Laboratories

1971 - 1972 Measurements of periodicities in the activity of the Opossum.
Antioch College

Publications as of Oct. 1982

Book Chapters

Lipetz, P.D. (1980) "DNA Superstructure, Development and Aging." In: National Institute of Aging: Biological Mechanisms of Aging. Schimke, R.T., ed., 290-315.

Lipetz, P.D. and Brash, D.E. (1982) "Relationship of DNA Tertiary and Quaternary Structure to Carcinogenic Processes." In: Adv. Cancer Res. 36, 165-210.

Lipetz, P.D., Smith-Sonneborn, J., and Stephens, R.E. "Natural and Induced Inhibition of Repair of DNA Superstructure in Eukaryotic Cells." In: DNA Repair and Its Inhibition (eds., Collins, A., Johnson, R.T., and Copple, C.), 1982, in press.

Lipetz, P.D., Smith-Sonneborn, J., and Stephens, R.E. "In Vivo Age Related Decline in Chromatin Repair of Human Lymphocytes" In: Modern Research in Aging: Intervention in the Aging Process, (eds., Adelman, Richard; Baker, George; Christofalo, Vincent; and Roberts, J.), Alan Liss, Inc., N.Y., 1983, in press.

Smith-Sonneborn, J., Lipetz, P.D., and Stephens, R. E. "Novobiocin and Kinetin Modulation of Paramecium Life Span" In: Modern Research in Aging: Intervention in the Aging Process, (eds., Adelman, Richard; Baker, George; Christofalo, Vincent; and Roberts, J.), Alan Liss, Inc., N.Y., 1983, in press.

As Editor

Series Editor, State University of New York Press, Cell Biology Series.

Refereed

Lipetz, P.D., Brash, D.E., Joseph, L.B., Jewett, H.D., Lisle, D.R., Lantry, L., Hart, R.W., and Stephens, R.E. "Determination of DNA Superhelicity and Extremely Low Levels of DNA Strand Breaks in Low Numbers of Nonradiolabeled Cells by DNA-4'6 Diamidino-2-phenylindole Fluorescence in Nucleoid Gradients," Analytical Biochemistry 121, 339-348, 1982.

Lipetz, P.D., Murphy, M.P., Jewett, H.D. and Stephens, R.E. (1982) "12-O-Tetradecanoyl-Phorbol-13-Acetate (TPA) Decreases Chronic Lymphocytic Leukemia B Lymphocyte DNA Negative Superhelicity To Normal Levels. Adv. in Comparative Leukemia Research 1981, 591-592.

Stephens, R.E., Joseph, L.B., Daniel, B.F., Lipetz, P.D., and Millette, J.R., Interactions of Chrysotile and Benzopyrene in a Cell Culture System, Environmental Health Perspectives, in press.

Joseph, L.B., Stephens, R.E., Lipetz, P.D., and Newman, H.A.I., Morphological Transformation In Vitro of Normal Human Fibroblasts, Environmental Health Perspectives, in press.

Lipetz, P.D., "Compartment Model of Carcinogenic Promotion" Doctoral Dissertation, Ohio State University, 1978.

Lipetz, P.D., Galsky, A., and Stephens, R.E. "Ti Plasmid DNA Negative Superhelicity Modulates Agrobacterium tumefaciens Induced Tumorgenesis." DNA 1, 95, 1981.

Lipetz, P.D., Stephens, R.E., and Smith-Sonneborn, J. "Altered DNA Superhelicity and Novobiocin Sensitivity With Age." XII. International Congress of Gerontology 2, 127, 1981.

Lipetz, P.D., Hart, R.W., and Stephens, R.E. (1980) "Decreased DNA Negative Superhelicity With Age." In: Proceeding of the Fund For Integrative Biomedical Research Conference on Biomarkers In Aging.

Lipetz, P.D., Lowney, C.S., Mhaskar, D. and Hart, R.W. "DNA Superhelicity: A Possible Mechanism for Polyamine Modulation of Procaryotic Nucleic Acid Synthesis." In: Gene Structure and Expression, Dean, D.H., Johnson, L.F., Kimball, T.C. and Perlman, P.S. eds. The Ohio State University Press, Columbus, Ohio, 345, 1979.

Mandalwala, R.H., Campbell, R.M. and Lipetz, P.D. "An Arrangement for the Study of Fish Activity Using Photosensitive Devices." 26th Annual Conference on Engineering in Medicine and Biology, 261, 1973.

Nonrefereed

Lipetz, P.D., Ford, K.E., Icard, C., Liepkaln, V., Yates, A.J., and Stephens, R.E. (1980) "Novobiocin and Nalidixic Acid Inhibition of Presumptive Gyrase Activity in Human Cells." J. Cell Biol. 87, 49a.

Lipetz, P.D., Brash, D.E., Joseph, L.B., Jewett, H.B., Hart, R.W., Lipetz, L.E., and Stephens, R.E. (1980) "Fluorescent Detection of DNA Strand Breakage in Nucleoids Derived from a Subpopulation of Aging Human Fibroblasts. Fed. Proc. 39, 1739.

Lipetz, P.D., Kornacker, K. and Hart, R.W. (1979) Compartment Model of Carcinogenic Promoter Activity." Fed. Proc. 38, 702.

Stephens, R.E., Joseph, L.B., Daniel, B.F., Lipetz, P.D., and Millette, J.R., Interactions of Chrysotile and Benzopyrene in a Cell Culture System, 2nd International Workshop on the In Vitro Effects of Mineral Dusts, Arkadelphia, Ark., 1981.

Joseph, L.B., Stephens, R.E., Lipetz, P.D., and Newman, H.A.I., Morphological Transformation In Vitro of Normal Human Fibroblasts, 2nd International Workshop on the In Vitro Effects of Mineral Dusts, Arkadelphia, Ark., 1981.

Lipetz, P.D., Ford, K., Icard, C., Liepkalns, V. Yates, A.J., Hart, R.W., Stephens, R.E. (1980) "Indirect Evidence for Encaryotic Gyrase (Naladixic Acid and Novobiocin Inhibition of Scheduled and Unscheduled DNA Synthesis)." J. Cell Biol. 87, 49a.

In Preparation

Lipetz, P.D., Boyle, S.M., Mhaskar, D.N., Lowney, C.S., Modak, S.P., Stephens, R.E., and Hart, R.W. "Polyamine Inhibition of DNA Superhelicity Relaxing Activity In Vitro and In Vivo".

Galsky, A.G., Lipetz, P.D., and Stephens, R.E. "Polyamines Modulate Kinetin Mediated Plant Senescence".

Smith-Sonneborn, J., Stephens, R.E., and Lipetz, P.D. "Novobiocin Inhibition of Dark Repair and Longevity in Paramecium".

Major Presentations

1982	Conference on Intervention in the Aging Process "In Vivo Age Related Decline In Chromatin Repair of Human Lymphocytes" "Novobiocin and Kinetin Modulation of Paramecium Life Span" Boston University
1982	U.S. House of Representatives, Washington, D.C. "Naturally Occurring Variations In Chromatin Repair Capacity" Investigations and Oversight Subcommittee on Science and Technology
1982	International Workshop on DNA Repair "Inhibition of DNA Tertiary and Quaternary Structures in Eukaryotic Cells" Cambridge University
1980	Gerontological Society Scientific Meeting Symposium on Longevity Assurance Processes "Control of Aging and Development By Higher Order DNA Structure"
1980	Gordon Conference on Aging "Alternations in DNA Superhelicity and DNA Superhelical Modifying Enzymes With Age"
1980	National Institute of Aging Conference on the Biological Mechanisms of Aging invited participant
1980	Fund for Integrative Biomedical Research Conference on Biomarkers In Aging "DNA Superhelicity and Aging"
1979	National Paraplegia Foundation Mechanisms of Longevity Extension - DHEA "Aging, Carcinogenic Promotion, and DNA Superhelicity"

Other Presentations 1980-82

September 1982	Syva-Syntex, Palo Alto, California "Commercial Applications of DNA Superstructure"
January 1982	DuPont, Wilmington, Del. "Commercial Applications of DNA Superstructure"
July 1981	XIIth International Congress of Gerontology Hamburg, Germany "Altered DNA Superhelicity and Novobiocin Sensitivity with Age"

April 1981	Maharishi International University Aging Conference "DNA Superhelicity: A Modulator of Aging and Neoplasia"
March 1981	Ohio State University Columbus, Ohio "DNA Superhelicity: A Modulator of Aging and Neoplasia"
March 1981	University of California Los Angeles Los Angeles, California "DNA Superhelicity: A Modulator of Aging and Neoplasia"
February 1981	First International Recombinant DNA Congress San Francisco, California "Ti Plasmid DNA Negative Superhelicity Modulates Agrobacterium tumefaciens Induced Tumorigenesis"
December 1980	University of Kentucky Sanders Brown Gerontology Institute Lexington, Kentucky "DNA Superhelicity and Aging"
December 1980	Fund for Integrative Biomedical Research "The Role of Mitochondrial In Superhelicity in Aging"
December 1980	Fund for Integrative Biomedical Research Microconference on "Death" Hormones Washington, D.C. "Hormonal Modification of DNA Superhelicity"
November 1980	American Society for Cell Biology Cincinnati, Ohio "Novobiocin and Nalidixic Acid Inhibition of Presumptive Gyrase Activity in Human Cells
October 1980	Bowling Green State University Bowling Green, Ohio "DNA Superhelicity and Aging"
April 1980	FEBS - Biophysical Society New Orleans, La. "Fluorescent Detection of DNA Strand Breaks in Nucleoids Derived From Subpopulation of Aging Human Fibroblasts"

STATEMENT OF PHILIP D. LIPETZ, PRESIDENT, GENERAL MOLECULAR APPLICATIONS, INC., ACCOMPANIED BY JOHN L. GRAY, ESQ., LAW FIRM OF EMENS, HURD, KEGLER & RITTER, COLUMBUS, OHIO

Mr. LIPETZ. Thank you, Mr. Chairman, and members of the committee. I wish to express my appreciation to the chairman, Albert Gore, and to Congressman Bob Shamansky for giving me the opportunity to present to the subcommittee the results of preliminary research investigations which I believe are very pertinent to the scope of the subcommittee's task in eliminating hazardous conditions in the workplace and to provide input to the report being prepared by the Office of Technology Assessment.

The committee, Members of Congress, the staff, and OTA are to be commended on their investigations in this area.

General Molecular Applications, Inc., is a wholly owned subsidiary of Omnimax, Inc., a public company which is engaged in evaluating new technology and coordinating the efforts of inventors and scientists in conducting research and development, leading to the development of commercial products.

Among its activities, Omnimax, Inc., through a wholly owned subsidiary, U.S. Energy Resources, Inc., is engaged in a research program developing a new type of thermoelectric generator which utilizes waste heat from utilities and certain manufacturing plants and converts this heat energy into electric energy. We will have some additional results on this process by the end of next year.

We are particularly appreciative of the action taken by the Congress to encourage private sector capital investment in research and development. This has enabled preliminary financing of both General Molecular Applications, Inc., and U.S. Energy Resources, Inc., to occur and also supports continuation of research programs.

The availability of such inducements will enable not only Omnimax, Inc. and its subsidiaries, but many other private companies, to continue their research and to embark on new research and development projects that could lead to other products.

Speaking parochially, since I am located in Columbus, Ohio, I also want to commend Congressman Shamansky for his efforts to encourage research and development activities in the establishment of high-technology companies in the central Ohio area by building on an environment of research and information resources, which ranks behind only Washington and Moscow in the world because of the presence of Battelle Memorial Institute Laboratories, Chemical Abstracts, and the Ohio State University in Columbus, Ohio.

I was particularly pleased to note in the Columbus Citizen-Journal of September 6, 1982, the editorial which Congressman Shamansky previously referred to.

General Molecular Applications, Inc., has been conducting research on a variety of fronts in the biotechnology area, including antiaging research, new methods of gene insertion in the DNA molecule and ways to improve the yield of desired product in genetic engineering. However, the discoveries relating to the prevention of damage to workers from hazardous substances will result in General Molecular Applications, Inc.'s first major commercial product.

The research results recently achieved by General Molecular Applications, Inc., are particularly pertinent to the mission of this subcommittee as set forth in the above editorial comment.

We believe the research results thus far constitute a significant development in the evaluation of worker exposure risk in certain industries.

We have developed an extremely sensitive procedure to measure DNA strand breaks and resulting changes in chromatin structure in human white blood cells—hereinafter referred to as DNA damage—and to measure the variations in the ability of different individuals to repair such DNA damage and restore actual DNA protein structure.

You will recall that DNA refers to deoxyribonucleic acid, which determines the type and function of a cell. Chromatin is the packaging of the DNA into a protein complex which determines the exact products produced by the cell. By means of the proprietary procedure which we have developed, it appears that we detect as few as one DNA strand break in 165 million DNA base pairs.

Human beings are known to differ widely in their physiology, and the consequence of these differences is that individuals differ in their ability to repair a given level of DNA damage induced by genetic toxins. It is unrepaired genetic damage that is the primary health hazard and therefore these differences in repair capacity are extremely significant. If an individual has an inherent deficiency in his ability to repair DNA damage, then an exposure which otherwise would have no significant health consequences might result in unforeseen pathologies.

Individuals with extremely impaired ability to repair DNA damage are susceptible to increased rates of carcinogenesis and aging. Extreme cases of impaired ability to repair DNA are usually accompanied by other symptomologies and so may be readily identified.

However, an individual may have sufficient levels of DNA repair to withstand the amount of DNA damage induced by normal environments, but not enough DNA repair capacity to withstand the otherwise acceptable levels of DNA damage induced by incidental chemical or radiation exposure. Such an individual, totally unlike his normal counterpart, will run a significant health risk by such exposure.

To conduct our measurement of repair capacity, white blood cells were collected from subjects and then subjected to x-irradiation of 100 rads of X-irradiation.

To put this in focus, this is approximately 1,000 times the amount of radiation which one would receive in an ordinary chest X-ray. Three hundred and fifty rads of whole body radiation will kill one-half of the population exposed thereto. We then measured the time it took to repair the damage induced by the X-irradiation.

Restoration of DNA strand breaks and the associated protein DNA complex was measured immediately after radiation after 2 hours and after 5 hours.

Sixty-seven percent of the samples tested exhibited complete repair after 2 hours, while 20 percent had not been repaired after 2 hours.

Thirteen percent of the population did not exhibit complete repair after 5 hours. These results are reproducible. Thus, it may be concluded that approximately one-third of the population studied has difficulty in repairing this form of DNA damage. Thirteen percent of the population may not be able to repair the damage at all within an acceptable period of time. See appendix A.

Of course, further research and additional sampling must be done, but results to date would indicate that at least 13 percent of the population, and possibly as high as one-third of the population, should not necessarily be exposed to radiation and toxic chemicals that could cause DNA damage.

Since DNA damage, especially from radiation, is associated with cancer and premature aging, it is important to prevent susceptible individuals from incurring such exposure. This has application not only in industrial locations, such as chemical plants and the nuclear industry, but also in the military.

In addition to the use of this new technology as a screening tool to protect those members of society who have an inherent incapability to repair DNA damage, this technology will also quantitate the degree of damage induced by an accidental exposure.

If we have previously measured the ability of the individual to repair DNA damage, early sampling of that individual's blood by means of the technology which we have developed will enable us to determine the extent of the damage to the individual, if any.

A specialized application of our DNA damage blood test involves military situations where a soldier might be exposed to either radiation or genetic toxins, such as agent orange.

In such a case, it is important to quantitate the degree of such exposure so that the onset of acute symptomologies can be predicted, and so that, if possible, fresh personnel can be utilized in any situation which would involve further exposure.

It is also important to expose only these individuals with normal DNA and chromatin repair. This will prevent an otherwise acceptable exposure from damaging sensitive individuals.

Such a program would effectively counter charges from individuals and veterans groups that the military has displayed a lack of concern for the consequences of exposure to such genetic toxins as agent orange. In addition, such a technique would quantitate the actual biological exposure of military personnel in situations such as nuclear submarines, rather than the average background radiation level.

Removing sensitive individuals from these situations will also raise the safety level without changing the exposure. General Molecular Applications, Inc.'s technique can be adapted to automated, portable units.

In summary, therefore, General Molecular Applications, Inc., with the active support of Omnimax, Inc., has developed a new technology which can be very useful in detecting the ability of DNA to repair damage caused by radiation or toxic chemicals; and, as we move forward with the development of commercial diagnostic instrumentation, we would appreciate the opportunity to keep the subcommittee, OTA, the military, and other concerned Federal agencies informed of our progress.

In the meanwhile, on behalf of Omnimax, Inc., General Molecular Applications, Inc., and myself, I would like to express my appreciation to the subcommittee for the opportunity to appear before it. I would be happy to answer any questions.

Thank you, Mr. Chairman.

[The prepared statement of Mr. Lipetz follows:]

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TESTIMONY OF DR. PHILIP D. LIPETZ, PRESIDENT, GENERAL MOLECULAR APPLICATIONS, INC., COLUMBUS, OHIO, AND PRESIDENT OF OMNIMAX, INC., PHILADELPHIA, PENNSYLVANIA, TO THE INVESTIGATIONS AND OVERSIGHT SUBCOMMITTEE OF THE COMMITTEE ON SCIENCE AND TECHNOLOGY OF THE U.S. HOUSE OF REPRESENTATIVES ON OCTOBER 6, 1982.

I wish to express my appreciation to Chairman Albert Gore, Jr. (D-Tenn) and to Congressman Bob Shamansky (D-OH) for giving me the opportunity to present to the subcommittee the results of preliminary research investigations which I believe are very pertinent to the scope of the subcommittee's task in eliminating hazardous conditions in the work place and to provide input to the report being prepared by the Office of Technology Assessment. The Committee, Members of Congress, the staff, and OTA are to be commended on their investigations in this area.

General Molecular Applications, Inc. is a wholly-owned subsidiary of Omnimax, Inc., a public company which is engaged in evaluating new technology and coordinating the efforts of inventors and scientists in conducting research and development, leading to the development of commercial products. Among its activities, Omnimax, Inc., through a wholly-owned subsidiary U.S. Energy Resources, Inc., is engaged in a research program developing a new type of thermoelectric generator utilizing waste heat from utilities and certain manufacturing plants and converting this heat energy into electric energy. We will have some additional results by January or February of 1983.

We are particularly appreciative of the action taken by Congress to encourage private sector capital investment in research and development. This has enabled preliminary financing of both General Molecular Applications, Inc. and U.S. Energy Resources, Inc. to occur, and also to support continuation of research programs.

The availability of such inducements will enable not only Omnimax, Inc. and its subsidiaries, but many other private companies to continue their research and to embark on new research and development projects that could lead to other products.

Speaking parochially, since I am located in Columbus, Ohio, I also want to commend Congressman Shamansky for his efforts to encourage research and development activities in the establishment of high-technology companies in the central Ohio area by building on an environment of research information resources, which ranks behind only Washington and Moscow in the world because of the presence of Battelle Memorial Institute Laboratories, Chemical Abstracts, and The Ohio State University in Columbus, Ohio.

I was particularly pleased to note in the Columbus Citizen-Journal of September 6, 1982, the following editorial describing the activities of this committee:

Columbus Citizen-Journal
A SCRIPPS-HOWARD NEWSPAPER
RICHARD R. CAMPBELL, Editor • SEYMOUR RAIZ, Managing Editor
GREGORY A. DEMBSKI, General Manager
34 S.Third St., Columbus, Ohio 43216
Telephone 461-5000
Give Light And The People Will Find Their Own Way
Page 6 MONDAY, SEPTEMBER 6, 1982

Genetic testing

Advancing medical science continues to raise ethical and legal questions earlier generations did not worry about.

Specialists can check a person's genes or chromosomes to determine if he is prone to a particular disease or ailment. Although genetic testing is just getting started, the technique is sure to become more common.

About 60 major U.S. corporations, responding to an anonymous questionnaire from Congress' Office of Technology Assessment, say they plan to begin testing their workers in the next five years. Six others are testing now.

U.S. Rep. Albert Gore, D-Tenn., chairman of the House oversight subcommittee on science and technology which ordered the survey, termed the finding surprising.

On the one hand, the technique can be a marvelous tool to protect the health of workers by determining if they are genetically predisposed to serious illnesses that could be caused by chemicals and other materials used in the workplace, Gore said.

It could also be a vehicle for invidious discrimination because certain genetic traits often are linked to a particular ethnic group, sex or race, the congressman noted.

Some critics are concerned that companies will use genetic screening to cut corners on safety by hiring only workers who are not susceptible to certain diseases.

If genetic testing ever becomes the legal issue Gore thinks it might, laws can be written to prevent misuse of the technique.

In any case, this is one instance where a congressional committee should be commended for exercising foresight as well as oversight.

General Molecular Applications, Inc. has been conducting research on a variety of fronts in the biotechnology area, including anti-aging research, new methods of gene insertion in the DNA molecule and ways to improve the yield of desired products in genetic engineering. However, the discoveries relating to the prevention of damage to workers from hazardous substances will result in General Molecular Applications, Inc.'s first major commercial product.

BEST COPY AVAILABLE

The research results recently achieved by General Molecular Applications, Inc. are particularly pertinent to the mission of this subcommittee as set forth in the above editorial comment.

We believe the research results thus far constitute a significant development in the evaluation of worker exposure risk in certain industries.

At General Molecular Applications, Inc. we are currently exploring three lines of research in preventive human genetic toxicology. The first line of research utilizes blood samples to quantitate, with unprecedented sensitivity, the extent to which exposure to genetic toxins has altered the DNA and chromatin structure of each individual worker. As you will recall, DNA refers to deoxyribonucleic acid, which determines the type and function of a cell. Chromatin is the packaging of the DNA into a protein complex which determines the exact products produced by the cell. The second line of research is preventive genetic toxicology and involves a simple blood test which predicts each individual's susceptibility to illness induced by genetic toxins, such as radiation or chemicals. Preliminary use of this test indicates that more than 33 percent of the population may be unusually sensitive to genetic toxins and hence have a higher incidence of environmentally induced carcinogenesis. The third line of research is the development of prophylactic pharmaceuticals which increase an individual's ability to repair genetic damage induced by exposure to genetic toxins and hence prevent the onset of illness induced by

exposure to genetic toxins. Thus, General Molecular Applications, Inc. intends to provide services which will decrease the health hazards inevitably associated with vital elements of our industrialized society, such as chemical production, hydrocarbon-based energy sources, and nuclear facilities. These services will increase the safety of the work place.

General Molecular Applications, Inc. has developed a new technique for quantitating DNA strand breaks and resulting changes in chromatin structure in human lymphocytes (white blood cells), hereinafter referred to as "DNA damage". Variants of this technique can be utilized to indirectly quantitate other forms of DNA damage. DNA damage has been shown to correlate with, and probably be a causal factor in, many human pathologies including carcinogenesis and premature aging. Therefore, careful monitoring of an individual's effective biological exposure to such forms of DNA damage will allow at-risk individuals to be removed from possible hazards before the probability of incurring serious pathologies has become overwhelming. The sensitivity of the General Molecular Applications, Inc. technique is such that we can detect such DNA damage at levels of radiation which do not induce any immediate acute symptoms. Therefore, apparently healthy workers who are nevertheless at risk, can be identified. Previous attempts to prevent genetic toxicity have involved computing the average exposure in a worker's environment and do not take into account the variations induced in normal

performance of work. Our monitoring program solves the problems associated with previous attempts. Previous attempts to quantitate the extent of genetic damage, if any, incurred by the workers in such environments have been statistically impossible to interpret since they rely on inherently insensitive techniques such as sister chromatid exchange. The use of such insensitive techniques has resulted in much misinformation being disseminated on this subject.

Another specialized application of our DNA damage blood test involves military situations where a soldier has been exposed to either radiation or genetic toxins, such as Agent Orange. In such a case it is important to quantitate the degree of such exposure so that the onset of acute symptomologies can be predicted and so that, if possible, fresh personnel can be utilized in any situation which would involve further exposure. Such a program would effectively counter charges from individuals and veterans groups that the military has displayed a lack of concern for the consequences of exposure to such genetic toxins as Agent Orange. In addition, such a technique would quantitate the actual biological exposure of military personnel in situations such as nuclear submarines, rather than the average background radiation level. General Molecular Applications, Inc.'s technique can be adapted to automated, portable units.

Human beings are known to differ widely in their physiology, and General Molecular Applications, Inc.'s second line of research concerns the consequences of differences among

individuals in their ability to repair a given level of DNA damage induced by genetic toxins. It is unrepaired genetic damage that is the primary health hazard and therefore these differences in repair capacity are extremely significant. If an individual has an inherent deficiency in his ability to repair DNA damage, then an exposure which otherwise would have no significant health consequences might result in unforeseen pathologies. Individuals with extremely impaired ability to repair DNA damage are susceptible to increased rates of carcinogenesis and aging. Extreme cases of impaired ability to repair DNA are usually accompanied by other symptomologies and so may be readily identified. However, an individual may have sufficient levels of DNA repair to withstand the amount of DNA damage induced by normal environments but not enough DNA repair capacity to withstand the otherwise acceptable levels of DNA damage induced by incidental chemical or radiation exposure. Such an individual, totally unlike his normal counterpart, will run a significant health risk by such exposure.

General Molecular Applications, Inc. has developed a simple blood test to determine an individual's capacity for DNA repair. By means of the proprietary procedure which we have developed, it appears that we detect as few as one DNA strand break in one hundred and sixty-five million DNA base pairs. In conducting this research, the cell sample was collected from subjects and then subjected to radiation of one hundred rads of x-irradiation. To put this in focus, this is

approximately one thousand times the amount of radiation which one would receive in an ordinary chest x-ray. Three hundred and fifty rads of whole body radiation will kill one-half of the population exposed thereto. We then measured the time it took to repair the damage induced by the x-ray.

Restoration of DNA strands and the associated protein DNA complex in the cell was measured immediately after radiation after two hours and after five hours. Sixty-seven percent of the samples tested exhibited complete repair after two hours while twenty percent had not been repaired after two hours. Thirteen percent of the population did not exhibit complete repair after five hours. These results are reproducible. Thus, it may be concluded that approximately one-third of the population studied has difficulty in repairing this form of DNA damage. Thirteen percent of the population may not be able to repair the damage at all within an acceptable period of time. (See Appendix A.)

Of course, further research and additional sampling must be done but results to date would indicate that at least thirteen percent of the population, and possibly as high as one-third of the population, should not necessarily be exposed to radiation and toxic chemicals that could cause DNA damage.

Such a variability in DNA repair capacity could explain why one worker may go for decades without any health problems while his coworker is constantly ill. General Molecular Applications, Inc.'s blood test would allow the identification

of such health risks and allow them to be transferred to safer employment categories. This test is not designed to identify hazardous work place situations but rather is designed to identify individuals for whom an otherwise acceptable work place is hazardous. An analogy would be preventing untreatable epileptics from becoming commercial airline pilots. It has been suggested that many elements of the petrochemical industry are already engaged in primitive forms of genetic screening to accomplish this goal. However, these tests are either biological or cytogenetic as set forth in the OTA report. General Molecular Applications, Inc.'s test is neither of these in that it examines chromatin damage and is over one hundred times more sensitive than previously possible without significant artifactual induction of DNA strand breaks. Therefore, General Molecular Applications, Inc.'s blood test can measure the repair capacity of isolated blood cells which have been exposed outside of the body to more physiologically relevant levels of DNA damage than the massive doses currently required by insensitive methodologies. The use of the General Molecular Applications, Inc.'s DNA repair blood test should lower health-related worker absenteeism and insurance claims and thereby result in lower operating costs for industry.

Such a test could also explain why only some individuals suffer significant health consequences as a result of exposure to Agent Orange or naval nuclear propulsion plants. If military personnel were routinely tested for classification according to

their ability to withstand DNA damage, then susceptible individuals could not be exposed to situations such as nuclear submarines. Furthermore, the adoption of such routine screening would demonstrate the military's concern for the genetic welfare of its personnel and go a long way towards silencing the criticism it has incurred because of Agent Orange and nuclear radiation sources.

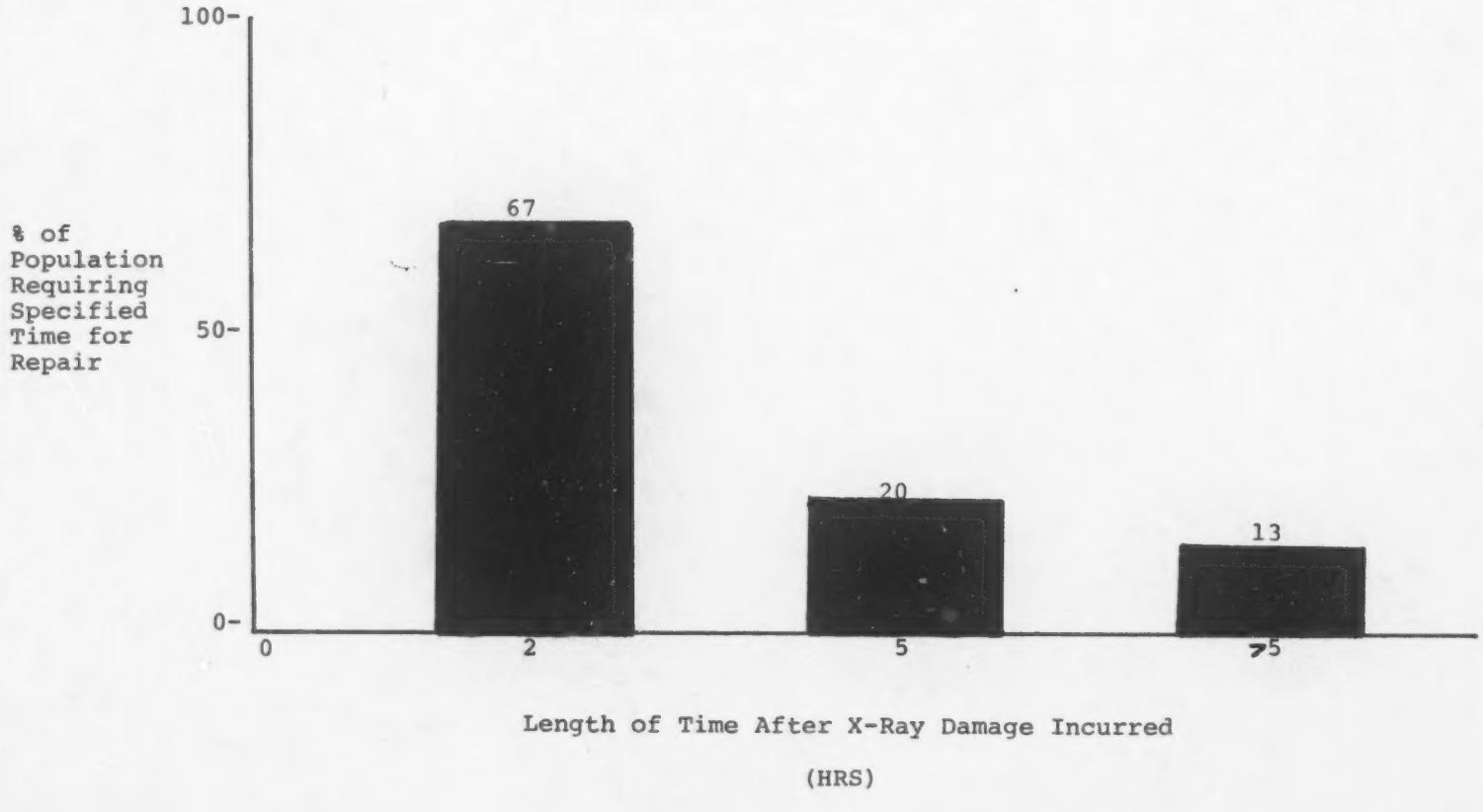
General Molecular Applications, Inc.'s third line of research is a long-term project to identify pharmaceuticals which will increase an individual's ability to repair DNA damage and hence increase the safety of prophylactically treated individuals later exposed to sources of genetic damage. Such pharmaceuticals might be used to treat individuals identified as being at risk via the General Molecular Applications, Inc.'s DNA repair blood test. Such pharmaceuticals might also be used to treat individuals undergoing radiation therapy or chemotherapy as a means of preventing damage to healty tissues. There are also many obvious military and civil defense applications of such pharmaceuticals. General Molecular Applications, Inc. has already identified two mammalian substances which have such a capacity. Basic research on these pharmaceuticals is proceeding under contract from General Molecular Applications, Inc.

Thus, General Molecular Applications, Inc., with the active support of Omnimax, Inc., is attempting to provide three integrated programs for the prevention of the illnesses associated with genetic toxicity. General Molecular Applications,

Inc. has already developed new techniques which allow unparalleled sensitivity in utilizing blood measurements to safely quantitate the degree of genetic damage incurred by an individual and to predict an individual's ability to repair genetic damage. These two tests allow for the first time, human measurements to direct sophisticated programs aimed at the prevention of genetic illness. Previously it has been only possible to identify grossly hazardous situations. Now it is possible to identify situations which otherwise might pass undetected until a major crisis occurs. Furthermore, General Molecular Applications, Inc.'s DNA repair blood test results in the identification of individuals who are unusually at risk and can allow for either their segregation from sources of risk or for obtaining their waiver to remain in such at-risk situations. It should be emphasized that such individuals are at risk in situations which would present no significant health hazards to other individuals. Both of these tests can be automated and have obvious military as well as industrial implications. Additionally, General Molecular Applications, Inc. has identified and is in preliminary stages of testing potential pharmaceuticals which should alleviate much of the negative factors associated with exposure to sources of genetic toxicity. This is the only integrated program of this sort in the world and it fills an obvious need in both industrial and military sectors. It is only by such an integrated multitiered approach that illness associated with genetic toxicity may be effectively prevented.

As we move forward with the development of commercial diagnostic instrumentation and other products of research, we would appreciate the opportunity to keep the subcommittee, OTA, the military, and other concerned federal agencies informed of our progress. In the meanwhile, on behalf of Omnimax, Inc., General Molecular Applications, Inc., and myself, I would like to express my appreciation to the subcommittee for the opportunity to appear before it. I would be happy to answer any questions.

APPENDIX A


100-
50-
0-
% of Population Requiring Specified Time for Repair
67
20
13
0
2
5
>5
Length of Time After X-Ray Damage Incurred
(HRS)

Mr. GORE. Mr. Shamansky.

Mr. SHAMANSKY. Thank you, Mr. Chairman.

Needless to say, I am always inordinately proud when someone from my home community, and especially those associated with Ohio State, come to testify before the subcommittee.

You mentioned potential application with respect to the military.

What has been the interest of the military in what you have done so far?

Mr. LIPETZ. We have had contact with representatives of the Army's Surgeon General Board and also informal contacts with the Office of Naval Research. They have not indicated a great degree of interest in the project. They initially did when I contacted them, and the product was simply a matter of quantitating the manner of DNA damage that had occurred.

However, in subsequent meetings, after we discovered there may be a susceptible subpopulation, the representatives that we talked to now did not profess any interest in the project at all. The later development may have somehow influenced their decision.

Mr. SHAMANSKY. Are you saying to the extent that the military learned that they might have a problem if they use your technique, let's speculate, though, and with your counsel next to you, we understand about hypothetical situations; so the possibility would be that to the extent that the military found out that they could measure military population that had a high degree of exposure to a problem, they then sort of denied the existence of the problem by walking away from it?

Mr. LIPETZ. I cannot speculate as to the motivation of the individuals involved.

I am sure that they are very much concerned with the health and safety of the military personnel.

Mr. SHAMANSKY. With respect to your particular experience here, your testimony is——

Mr. LIPETZ. My testimony was that I was initially invited to submit a proposal when the technique involved quantification of DNA strand breaks, and when I later presented the data as explained to the subcommittee I did not have an equal degree of interest expressed.

Mr. SHAMANSKY. Did they give a reason for the change?

Mr. LIPETZ. No.

Mr. SHAMANSKY. Did you inquire?

Mr. LIPETZ. Yes.

Mr. SHAMANSKY. Can you make available to the committee your contacts and your correspondence?

Mr. LIPETZ. I would be glad to make available to the committee the names of the representatives that we met with.

Mr. SHAMANSKY. It would flush out your testimony.

Now, it seems to me, Dr. Lipetz, that once you learn that you can measure the susceptibility of these things, is there a good body of scientific data that relates the existence of this information and conditions that flow therefrom.

You talked about aging and carcinogenesis; how precise is the correlation?

Mr. LIPETZ. In the case of extreme cases such as individuals with genetic syndrome such as xeroderma pigmentosium, which is ac-

companied by the ability to repair, they do have an extremely high incidence of carcinogenesis induced by such exposure.

There are other syndromes accompanied by high rates of carcinogenesis.

However, until we develop this test, nobody has been able to identify people who have moderate levels of inability to repair who otherwise would seem to be normal.

Obviously, the next stage of research in the GMA program is to take familial histories and establish the exact degree of correlation of this moderate degree of exposure.

Heretofore, there has been no evidence that there were people who were susceptible other than perhaps epidemiological evidence that some people seemed to come down with cancer in groups of extreme susceptibility.

However, we have the first evidence, and, therefore, there does remain a certain degree of clinical work to be done.

Mr. SHAMANSKY. What has your relationship been, if any, with the National Cancer Institute and the American Cancer Society?

Mr. LIPETZ. My particular relationship has been none.

They do very good work, and they were not asked to sponsor this work, so they have not turned it down or in any way passed judgment on it, either positively or negatively.

Mr. SHAMANSKY. I notice in your biography, exceedingly interesting, your publications, how much have you published the results of your work, and have you gotten a response from the scientific community?

Mr. LIPETZ. I have presented the data that I just gave to you at an international workshop in Cambridge, England, on inhibition DNA repair, and this is what we would classify an analogy-occurring inhibition.

That work should be published at the end of the year, and as to the response of my colleagues, the only way I could characterize it was extremely interested, and, of course, they want more clinical data, which I would entirely agree with.

However, they accepted the data, and it is being published, which, to a degree indicates a certain degree of acceptance.

Mr. SHAMANSKY. Is further research being conducted to provide the additional data which your scientific colleagues say they need or want?

Mr. LIPETZ. Within the limits of the general molecular application budget, we are putting all of our resources——

Mr. SHAMANSKY. Are you aware of any parallel research in this area?

Mr. LIPETZ. We are the only ones in the world currently able to detect this sort of DNA damage and repair.

Mr. SHAMANSKY. Are you familiar with any research which correlates the lack of ability to repair and a particular illness?

Mr. LIPETZ. Yes; my favorite study is an animal study performed—because you won't want to try to induce carcinogenesis in a human—performed on fish at Oak Ridge Laboratories by two individuals, Ronald Hart and Richard Setlow. They took tissue from a fish, exposed it to DNA damage, and via a method where you can remove just that form of DNA damage and do nothing else to the

cell, either removed just that form of DNA damage or left it in, and then put the tissue back in the fish.

All those individuals that had the DNA damage left in it, developed cancers, tumors, and those individuals that had the damage removed, did not develop tumors. So this was evidence of a causal relationship.

Mr. SHAMANSKY. You were present, I believe, when the earlier panel of witnesses, the earlier witness, and Dr. Newall was here, give the criteria acceptable in scientific circles and predictability and reliability—I am using words I am not quite sure of—how do you rate your test?

Has your testing procedure met the rigorous intellectual scientific standards of the medical and scientific community?

Mr. LIPETZ. It has already been accepted and published that our test is over 100 times more sensitive than other tests.

Mr. SHAMANSKY. That is a relative thing, but if your test is not very good, the 100 times may not be very good, itself.

Mr. LIPETZ. A certain amount of clinical work is yet to be done before any legislation using this test; however, this is the first evidence that there may be a susceptible subpopulation in the human group that are unusually susceptible to carcinogenesis.

Therefore, the possible health hazard posed by this group is so significant that I feel that more research should be done to establish exactly the causality behind this, and then to act appropriately.

Mr. SHAMANSKY. Do you have any plans to present that thesis on what you feel should be done, to the National Institute on Cancer?

Mr. LIPETZ. Currently, as far as I know, if I, understand the particular situation that we have now, have the work sponsored by NCI, I lose the proprietary rights, and we do intend to eventually market this test.

Mr. SHAMANSKY. Yes, and as a lawyer, I have no problem with your protecting your proprietary interest. The point I am making, given the existence of the test, that would not preclude the National Cancer Institute from utilizing the tests?

Mr. LIPETZ. I would welcome it.

Mr. SHAMANSKY. Have you presented this to them?

Mr. LIPETZ. No.

Mr. SHAMANSKY. They are not familiar with this, as far as you know?

Mr. LIPETZ. If they chose to do the work independently, I would welcome such an examination. However, as far as applying for funds for myself, I have to——

Mr. SHAMANSKY. I understand. I mean about their using their own funds, utilizing your test?

Mr. LIPETZ. Yes, the standard procedure would be—now, the standard procedure would be generally what would occur upon publication of our paper which is in press; it would become better known to the scientific community, and then they would act appropriately on it. If the subcommittee did not have this hearing going on at this time, I would not have chosen a public forum to talk about this. However, I have presented it to a scientific group already, and it has been subjected to their evaluation. Therefore, it is

proper to present it, but the timing is solely dictated by the needs of the committee.

Mr. SHAMANSKY. Given your experience, what has been your experience with responses from other parts of the scientific community?

Mr. LIPETZ. For example, and this is purely anecdotal--and I cannot establish whether this gentleman is right or not—we have had gentlemen involved in cancer chemotherapy inform me that there is a certain group of leukemia that appears to be induced by cancer-chemotherapy, and they have wondered whether or not such individuals might be a susceptible subpopulation, since they have induced DNA damage; so, in other words, uses, they have become obvious to the people I have talked to. However, again, the research——

Mr. SHAMANSKY. For further research?

Mr. LIPETZ. That is correct.

Mr. GORE. Let me ask a couple of short questions here, and then I want to call on our colleague, Mr. Nelson.

The significance of what you are saying here is that your company, you say, has a test that does something that the OTA and the scientists in the field generally have thought was not possible for another 10 years.

That was the general projection?

Mr. LIPETZ. Two to ten years.

Mr. GORE. For the general range, but in this specific category, you are talking about individual differential genetic susceptibility predicted with a reasonable level of validity.

I know you don't want to disclose proprietary information, but can you give us some indication of what kind of advance your technique represents? Is this something that OTA was simply not aware of in doing its survey?

Mr. LIPETZ. Yes. I indicated very briefly in the testimony that our technique relied on a level between the two levels they looked at which were—they classified as—noncytogenetic and cytogenetic.

Ours fell in between. The basic problem with DNA is you have several feet of DNA that you have to fit into a very small cell, and, therefore, there is very exquisite packaging of that DNA that goes on before you hit a chromosonal level. Research has been concerned with the noncytogenetic level or the chromosone, which is a very gross level of the packaging, which does not take into account how the DNA level fell back on itself.

I have chosen to examine this intermediate level of organization, and because I am looking at a totally new level of organization, I have results which are unanticipated by either of the other two techniques.

Mr. GORE. Dr. Neil A. Holtzman at Johns Hopkins prepared for OTA a study of the screening applied to testing for genetic susceptibilities and came up with a 50-percent predictive value of a positive test result with techniques in this general area.

They may not be the same techniques that you are using, but is the 50-percent range compatible with what you are getting?

Mr. LIPETZ. We have not established the direct degree of correlation with our test yet so I can't state.

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Mr. GORE. You state that some 33 percent of your research population was unusually sensitive to genetic toxins. Correct?

Mr. LIPETZ. Yes.

Mr. GORE. What were the doses of radiation?

Mr. LIPETZ. One hundred rads, which would be sufficient to cause symptomology in a human being.

Mr. GORE. That is a fairly high dose, isn't it?

Mr. LIPETZ. Yes.

Mr. GORE. What would the percentage be for doses within the OSHA-accepted levels for radiation?

Mr. LIPETZ. Within the OSHA-accepted levels of radiation, I do not know of a direct test which can quantitate that. I think our test can quantitate in the area of 5 rads of radiation, which is beyond the OSHA-accepted levels.

Mr. GORE. What percentage would you get with 5 rads?

Mr. LIPETZ. I do not know.

Mr. GORE. But your test is sensitive enough; you could run that if you chose to?

Mr. LIPETZ. Yes.

Mr. GORE. Now, finally, by way of examining this technique, your tests have been done in culture or in vitro.

Is there a possibility that there is a missing link here, a big jump between the results you get in a petri dish and the kind of results that you would expect to get in a living organism?

Mr. LIPETZ. That is a very good question, Congressman.

If you take cells and establish them in a long-term culture, so that they undergo many different divisions and sort of establish a life of their own independent of the body; they do change, and they do adapt, and do have certain differences which are not the same as normal cells found in the body.

However, in the case of the GMA test, we are careful to take our cells and put them in culture solely for the purposes of separation. We run controls to make sure they have not divided and are still, as near as we can tell, cytogenetically the same as the cells found in the body.

So, while it does involve test tubes and culture media, we don't maintain a long-term culture; therefore, the term cultured cells is not applicable here, and we chose this approach to avoid the problems of cultured cells that you bring up.

Mr. GORE. Well, your answer assumes that the difference between cells in vitro and cells in vivo is principally the difference that occurred after they have divided in culture.

Are there not some other distinctions that might make it difficult to translate your results in living organisms?

Mr. LIPETZ. It is entirely possible. However, I believe that our test is the best available under the technology today and eliminates a lot of the problems you brought up.

Mr. GORE. All right. Fine. Well, I appreciate your response.

Mr. Nelson.

Mr. NELSON. OTA has said that it is going to take them perhaps 10 years to determine the differential genetic susceptibility. How long do you think it is going to take you to complete your research?

Mr. LIPETZ. Given money, if we make that supposition, which in our free enterprise system is not necessarily a correct supposition,

given sufficient amount of money, I think that we could have the clinical correlations and all of that sort of thing necessary for a complete evaluation completed in less than 2 years.

Mr. NELSON. And you are talking about money from both the private sector as well as Federal grants?

Mr. LIPETZ. Private sector, Federal grants, the military, whatever.

Mr. NELSON. Mr. Chairman, I think this is an exciting area, and you know, we have been at DNA research now for, well, when I was in the 10th grade at Malvern High School in 1957, my science research project was on DNA.

I was trying to take DNA from white mice and transfer it into black mice, and then do a skin graft and see if it would stick, and that is 25 years ago, and——

Mr. GORE. Well, how did Watson and Crick——

Mr. NELSON. Twenty-five years later, I would like to see the process continue and be as rapid as possible.

Mr. GORE. Thank you for being here. It is all naturally exciting and terrifying in some of its aspects, because these new techniques present us with brand new potentials, and our legal and ethical systems have not always kept pace with the new potentials that science throws upon us, and these technologies challenge our legal and ethical system for that reason.

Just as the world was unprepared for the consequences of nuclear weaponry as it was upon us, DNA research will confront humanity with new potentials that will challenge us quite discernibly, and that is why I think it is important for the Science Committee to try to look at the horizon and identify these challenges to society before they are full-blown and before they are so mature that we have trouble dealing with them.

We want to try to identify them early, and we appreciate you, Dr. Lipetz, being here.

Mr. NELSON. If the gentleman would yield, I appreciate you raising that issue. There is potential for harm in our society, but there is a great deal of potential for good as we start to unravel the very source of life as perhaps one of the means to cure disease, and so I appreciate you trying to look ahead and anticipate what are going to be the challenges to society.

Mr. SHAMANSKY. Mr. Chairman, if I may, I would like to note that Dr. Lipetz was accompanied by John Gray, his counsel, but I would like to say that Mr. Gray is a lawyer, and he was for many years associated with Battelle Memorial Institute, and his last post was vice president, I believe.

In the area of science and technology we have been pursuing here, there is a lot of talent in this country that part of our job is to utilize and bring to the attention of both the world and the country, and amongst our own communities, so I very much appreciate the opportunity that you presented to the witnesses today to address this important matter. Nice to have you with us, Doctor.

Mr. GORE. Thank you, Congressman Shamansky, for bringing a greater awareness to the fact that Columbus, Ohio is emerging as one of the nubs of science and culture.

Mr. SHAMANSKY. That is my message.

Mr. GORE. Thank you, both of you.

Our next witness is Prof. Howard Sloan, associate professor of pediatrics at Ohio State University, with a somewhat different view of some of the techniques that we have been discussing.

We would invite you to come forward to the witness table, Dr. Sloan.

Mr. SHAMANSKY. May I suggest, Dr. Sloan, that you pull the microphone right up close?

Mr. GORE. Without objection, your entire statement will be put into the record in full, and we invite you to proceed at this point.

STATEMENT OF PROF. HOWARD SLOAN, M.D., PH. D., ASSOCIATE PROFESSOR OF PEDIATRICS, OHIO STATE UNIVERSITY, COLUMBUS, OHIO

Dr. SLOAN. Being a professor, I often have a need for slides, and we are getting them ready over there.

Chairman Gore, Mr. Shamansky, staff and guests, it is a pleasure to testify before this committee, and I would like to raise a flag of caution into this hearing. In spite of dramatic advances that have been made over the last 20 years, medical science has not yet advanced to the point that a physician can routinely make a definitive diagnosis of even a very common disease on the basis of the results of a single laboratory test. Rather, accurate diagnoses are usually based on the results of: a detailed history, a careful physical examination, and a battery of laboratory tests. Testing of individuals for their susceptibility to environmental hazards is probably best described as being in its infancy at this time. I would like to put the field of testing genetic susceptibility to toxins into what I believe is an appropriate historical perspective by describing the development of our knowledge in a somewhat related field in which I have worked for almost 20 years. This field is termed the inherited metabolic diseases. An inherited metabolic disease may be defined as a genetically determined disorder in which there is an inherited defect in a specific chemical or biochemical reaction; this defect in turn leads to disturbed health of the affected individual. These diseases frequently provide exceptions to the general caveat that I state above. If a metabolic geneticist can obtain a piece of an appropriate tissue from the affected individual, one can often make a precise diagnosis with only a single test. In the past, accurate diagnoses of such conditions were dependent on the obtaining of a specimen of a vital organ, such as the liver or kidney, and occasionally, the obtaining of such a specimen was not possible until the patient died.

The advent of the techniques by which tissues can be kept alive in the laboratory, and even grown in test tubes and bottles, dramatically changed our approach to the diagnosis and study of inherited metabolic diseases. In this respect I should define the phrase in vitro; by this term scientists mean within glass, that is, observable in a test tube and therefore in an artificial environment. We contrast this with the term in vivo by which we mean, within the living body. As a background to my comments let me briefly trace the history of just a few of the critical developments which led to our present ability to maintain and grow human cells in an in vitro environment. In 1885 the first successful in vitro

maintenance of a tissue in a living state was achieved. Eighteen years passed before actual cell division in vitro was demonstrated; 4 years later it was demonstrated that cells in culture maintained some of their normal functions. From 1912 to 1946 there was a consolidation of knowledge, and techniques were developed for maintaining viable cells in culture without their loss to bacterial contamination or to disturbances in the composition of the growth medium. It was not until 1960 that the technique of tissue culture was first applied to genetic disorders, when the sex of a fetus was correctly ascertained. Seven years later, the first metabolic disease was correctly diagnosed in cultured cells. Since that time, the technique has been applied to almost 200 inherited metabolic disease. As a result of these advances, tissue biopsies are only rarely required today to establish the diagnosis of an inherited metabolic disease.

As we developed the ability to diagnose metabolic diseases in vitro, we had to overcome many pitfalls along the way. We learned that it was not adequate simply to obtain a piece of tissue from a patient, put it in a bottle, add the right liquid and wait for growth. Rather, we learned that a whole host of factors might adversely influence our ability to use in vitro techniques to establish accurate diagnoses. For example, it might be necessary to use age- and sex-matched controls. Great attention had to be paid to the environment in which the cells were grown. The appropriate medium (with optimal concentrations of various vitamins and growth factors) and temperature must be employed if reproducible values were to be obtained. The investigator had to be careful to control the humidity, the acidity and the composition of the air in which the cells were grown. The type of anesthetic used during the procurement of the specimen could effect the rate and quality of cellular growth. The glassware employed must be scrupulously clean—much cleaner than would be required for even the most demanding analytical studies. Moreover cultured cells must not be retained too long in culture before they are analyzed or erroneous values might be obtained. As an example of this problem let me show the next slide in which a growth curve of normal human skin cells—maintained in glass—is depicted. The rate of growth is very slow at first, accelerates at point b, becomes maximal at point c, and then falls off at point d; by point f, cells are actually beginning to die. If one were to measure, in normal cells, a chemical reaction which is diagnostic for a certain very rare disorder known as Niemann-Pick disease one would make a very disconcerting discovery. The level of the enzyme in a normal individual varies dramatically with the age of the cells in culture. At point a, the level is 1.6 units; at points b through f, the values are 3.7, 275, 180, 86, and 43, respectively. This example illustrates the need to exercise great caution when extrapolating from an in vitro result to an in vivo diagnosis. Similar and equally devastating effects on this type of an analysis can be experienced if one does not carefully control dozens of subtle variables. Even the way in which cells are harvested from the glass or plastic vessel in which they are grown may dramatically influence the results obtained. The time and temperature of the harvesting steps must be carefully controlled as must be the technique by which the cells are removed from the glass. Mechanical removal

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may yield quite different analytical results from those obtained following chemical removal of the cells.

Just when we thought that we had learned to control every important variable, two new problems were discovered. Seven years ago it was learned that growing tissue cultures in laboratories illuminated with standard daylight fluorescent lamps could result in serious cellular damage; I have recently visited the laboratories of two Nobel laureates and noticed daylight fluorescent lamps were in use in their tissue culture facilities. Moreover, only 2 months ago, it was reported that the brand of syringe into which a specimen was drawn could have major effects on the growth pattern of cultured cells. These defective syringes were entirely satisfactory for every other purpose except for the obtaining of blood specimens for use in tissue culture studies.

We have even found that batch of a material used to enrich the tissue culture growth medium and which is termed fetal calf serum is unique. As a result, the major suppliers routinely allow investigators to test different batches of this material, determine those which optimally stimulate cell growth, and restrict their purchases to those lots that are most efficacious. I should add that the mere fact that a heterogeneous substance such as fetal calf serum constitutes 10 to 20 percent of the volume of tissue culture media reflects the deficiencies in our knowledge regarding the minute requirements of cells maintained in culture.

We have also found that the lighting conditions that prevail during the time that the culture medium was prepared, can effect cellular growth. Surely, none of these problems are of significant concern with studies conducted in the intact human subject. It is of course possible that those advocating genetic screening for the effects of environmental toxins may learn to control all of the essential variables that the metabolic geneticist has learned to control through many years of careful study. I would submit, however, that it will probably take them as many years as it has taken us. Moreover, the metabolic geneticis has a finite and readily ascertained endpoint. In most metabolic diseases, the disorder becomes readily apparent within a few months to years, and we can therefore readily ascertain the validity of our diagnoses and make appropriate corrections for any errors we may have made. The environmental toxicologist is working in a veritable vacuum by comparison; the latent periods involved are measureable in terms of years, or even decades. By what criterion can they assess their results? How do they know when their speculations were valid and when they were totally invalid?

Among the more obvious problems associate with the in vitro testing of toxic agents, I would like to highlight just a few worrisome areas. In order to test a specific agent in a truly meaningful and representative fashion, one must understand the precise mechanisms by which that agent exerts it toxic effects. Such detailed knowledge of pathogenesis is extremely rare in the field of toxicology. As a result, one is not certain that one's in vitro tests are stressing the appropriate cell type or types within the putative target organ. Even a relatively simple tissue, such as the liver, has multiple cell types, each of which may, and probably does, have different toxic thresholds. Moreover, an agent may appear to be

toxic when it is evaluated acutely in an isolated test system, whereas a cell, or an organ, may naturally develop detoxifying mechanisms after prolonged exposure to a noxious agent. Such a process may be termed acquired tolerance. Finally, how can the toxicologist assure us that those cells which appear relatively resistant to a short exposure to a noxious agent will not be just as deleteriously affected by chronic exposure to this agent as are apparently "sensitive" cells?

Next, I would like to turn to what I believe is the most potentially dangerous aspect of biochemical and cytogenetic testing in the workplace. I term this problem the in vitro → in vivo jump. By this term I mean that an event which occurs in the test tube is definitely neither easily nor directly translated into one which may occur in the intact organism. Some of the problems I am about to consider are theoretical, although not at all unlikely. Others represent old and well established principles which are based on a multitude of practical examples. Extrapolations from in vitro experiments to in vivo conclusions are potentially invalid; I would agree, however, that if the experiments are properly controlled and the conclusions properly qualified, meaningful extrapolations can frequently be made. The onus in such situations, however, surely rests squarely on the shoulders of the extrapolator. The importance of a cell's environment cannot be overestimated. The growth pattern of normal cells is strongly inhibited by mere contact with other normal cells. No matter how meticulous we are in our attentio to details in the conducting of an in vitro experiment, we cannot, with today's knowledge, even closely approximate the host of chemical, hormonal, and neural influences that are exerted on cells growing and functioning in the intact animal. Therefore, the results of in vitro experiments provide, at most, guideposts; the leads provided must be supported by epidemiological, and, where possible, by in vivo experiments. The results, seasoned with a reasonable dose of cautious suspicion, must then be carefully analyzed and interpreted.

When one studies a reaction in vitro, one is dealing with a totally different set of selection pressures from those which exist in vivo. As I noted above, the whole organism may develop a tolerance to a noxious agent—a tolerance which an isolated cell, or group of cells, in an in vitro environment could never acquire. Such tolerance could be based on the existence or development of protective or detoxifying mechanisms in the target cell or in other cells of the body. For example, some biological catalysts (termed enzymes) are present in liver and kidney, but not in brain or skin. The latter tissues could therefore be readily protected by detoxification systems present in the former cells. There are several enzymes which are not present in resting blood cells or anmiocytes (cells found in the amniotic fluid bathing the fetus), but which are present in large amounts once these cells have been placed in culture in the appropriate environment for only a few hours. Moreover, the administration of some drugs stimulates the levels of enzymes involved in their detoxification. In addition, induced enzymnes may conceivably even convert a relatively inert chemical into a toxic chemical; this sequence may occur in an in vitro setting, but not in the intact individual. Although the occurrence of this latter sequence of events seems unlikely, it is certainly not im-

possible. It is also well known that cells isolated from the amniotic fluid undergo a dramatic change in their enzyme profile, even after only a few hours in culture. Such changes in a cell's enzymic profile could have significant impact on that cell's susceptibility to toxic agents. There is no assurance, at this stage of our knowledge, that all cells would experience the same degree of enzymatic change upon being placed into an in vitro environment. In addition, cells maintained in culture are highly susceptible, even under the most stringent conditions achievable in a purely research environment, to infection by viruses, mycoplasma and other organisms. Such infections carry with them the risk of insertion of foreign genes into the test cells. There is no certainty that all cells will be equally susceptible or equally exposed; therefore the utmost of precautions must be exercised by laboratories that plan to evaluate the toxicity of agents found in the workplace. Finally, any one of the multitude of potentially deleterious influences I have mentioned above may make cells from one individual appear more sensitive to a given noxious agent in vitro, while such abnormal environmental conditions would never occur in vivo.

A striking example of the unreliability of even highly specific and well established in vitro genetic tests is found in the clinical condition I have already mentioned—Niemann-Pick Disease. The next slide shows a picture of a child badly damaged by this disease. The patient died at 21 months of age following a relentless and devastating illness which totally destroyed his nervous system. By contrast, I have studied the child pictured in the next slide for 16 years. With even the most specific and sensitive laboratory tests that are available, this child cannot be differentiated from the child shown in the previous slide. His clinical course has, however, been quite different. He has done quite well in high school and college and is now entering his second year of law school. He is normal at this stage except for having an enlarged liver and enlarged spleen. Perhaps not entirely normal; he is now a first-year law student.

Mr. SHAMANSKY. Watch it, Doctor.

Dr. SLOAN. I do not believe that I need to stress to the members of this committee the potential dangers of fostering complacency by permitting an employer to claim that he or she has made the workplace safe by eliminating the potentially sensitive workers rather than the potentially noxious chemical agents. I would, however, like to point out the serious potential for violating a worker's privacy that is raised by genetic testing. The day is rapidly approaching when possessing a piece of a subject's skin would provide an unscrupulous individual with far more detailed information about that subject than could be obtained from a fingerprint and a high quality photograph. If we know enough about a person's genetic profile, we could exclude him or her from almost any job. It has been estimated that we all carry between three and eight lethal mutations; that is, mutations that are so deleterious that were we to have inherited one of them from each of our parents, we could not survive extrauterine life. The testing of environmental toxins is clearly an extremely important area of research and we must learn how to balance safety with economic practicality. I have no doubt

that some day in the future, this area of research will prevent a great deal of pain and suffering. Today is not yet that day.

We are now only in the information gathering stage, a stage which is the first step of any scientific research program and which must precede the enunciation of hypotheses. A scientific instrument or test can easily become a weapon if not used with great care. I suspect that many individuals will consider Congress to be obstructionistic if it prevents these preliminary studies from being used to deny employees a job or a promotion. I am, however, confident that Congress can effectively resist such criticism and that any delay will, in the long run, be as insignificant as that experience several years ago by the genetic engineers. The mandate delay provided the breathing space required for the establishment of effective safeguards for the public. Guaranteeing safe and publicly responsible research is not tantamount to obstructing research.

In conclusion, I would like to add that I find it highly unlikely that any single test will adequately evaluate the susceptibility of an individual to industrial or environmental toxins. Rather, we will need to employ a battery of sensitive, specific, and relevant tests.

Mr. GORE. I appreciate your testimony.

Congressman Shamansky.

Mr. SHAMANSKY. I am delighted to welcome Professor Sloan here. By pure coincidence we sat in virtually adjacent seats in the same bank of seats this morning, so we had a little discussion, although we did not get into anything like this.

I found your testimony, Professor Sloan, absolutely fascinating. It was an excellent exposition of some very complicated stuff, very concise and understandable to us lawyers, so we think that is a great step forward.

I cannot help but be fascinated as to the juxtaposition of your testimony with that of Dr. Lipetz, and I would like to pursue, because I do bring the experience of a business lawyer who has the responsibility to his clients to advise—I am talking about not a caricature of a bad businessman, but of an ethical, decent human being who says, "What is my obligation?" when he has a moral obligation to his employees and he has a legal obligation, which is where I come in as his lawyer.

What do you think I could advise my client on were he to come to me and say, "Oh, I have an opportunity based on Dr. Lipetz' work to determine the damage potential of an individual who may work in my plant?"

My question then assumes that you have some knowledge of Dr. Lipetz' work maybe in particular or just say in general, as you wish, how you feel competent to respond, do you believe—is it your professional opinion that there is enough there that a reasonable person should begin to respond, should take certain steps with respect to the kind of work that Dr. Lipetz is working on? And I would like you to comment on that.

Dr. SLOAN. This problem represents an example of the expression, there is many a slip twixt the cup and lip. I think that we are at a stage where we must gather this information. As I said in my testimony, in the first stage of developing a hypothesis, one had

best gather some experimental details and observations; then you can come up with a scientific hypothesis.

Mr. SHAMANSKY. Are you familiar with the work in the field now?

Dr. SLOAN. I have read two of Dr. Lipetz' articles.

Mr. SHAMANSKY. Can you place that work to the whole area in which you specialize in general, in other words, in the scientific community, assuming to the extent you are familiar with it?

Dr. SLOAN. I would put the work at this point as being similar to that of my field in the 1960's, early 1960's, when we were learning how to measure enzyme levels. It then took another 10 to 15 years before we were able to extrapolate from the values found for normal individuals to saying, "Aha, that child has the disease or that fetus will have the disease."

Mr. SHAMANSKY. Am I to infer from your answer that you feel, though, that his work is a step in a valid scientific——

Dr. SLOAN. I have no doubt from what I have read that he can measure DNA breaks. Let me give you an analogy. There are several different forms of administering certain drugs to asthmatics. We find that if you administer one of them by inhalation as opposed to intravenously you get a slightly increased level of oxygen in the person's blood. That result is desirable in asthma. It turns out, however, that the difference is a number of 2 out of 85. Statistically that difference is very significant. It turns out to be extremely significant, significance at the 95-percent confidence level, that is 1 chance in 10,000 at that level that the difference was by chance. But yet to the patient the difference has no clinical significance. It does not make a difference whether his blood oxygen is 87 or 89, but yet the drug given one way makes it higher. We must choose from other considerations which is the right way to give the drug to that patient.

We have a similar situation here. All sorts of things are being measured and many tests are being proposed. The question is how do we extrapolate from this information to what is valid, that is to what puts that individual at increased risk. We do not know, for instance, if a normal individual who has slightly more genetic breaks than another is at increased risk to cancer.

Mr. SHAMANSKY. Is work being done in the scientific community on answering the questions you are raising?

Dr. SLOAN. People are looking at it. Dr. Lipetz would say his technique is more sensitive than that of others.

Mr. SHAMANSKY. Are you familiar with any research pursuing similar techniques?

Dr. SLOAN. That approach, yes, there are lots of people who are looking at genetic breaks and trying to find this information. His technique does appear to be more sensitive than most.

Mr. SHAMANSKY. Therefore, if you had to predict the future, it would be a useful area of research?

Dr. SLOAN. It is an essential area of research.

Mr. SHAMANSKY. The research is being conducted at various stages?

Dr. SLOAN. That is correct.

Mr. SHAMANSKY. Based on your work, can you tell us about any, I will say, practical use of that technique now, given the fact that

it has a lot to go, there may be some useful aspect of it today, I mean useful in the sense of not just research, but health, environmental?

Dr. SLOAN. In preparation for appearing before this subcommittee I spoke with many scientists around the country, and my discussions were quite surprising. Most of my colleagues were unaware that industry was as far along as I have learned that they are, and the one word which was consistently used by these scientists, people who have been working in the field of genetics for many years, was "premature."

Mr. SHAMANSKY. I am fascinated. You just said that the scientists were unaware of what industry was doing; correct?

Dr. SLOAN. I am saying that geneticists were unaware how far along it was.

Mr. SHAMANSKY. That itself raises an interesting question to me. You have industry, and I think not irresponsibly, moving along, and yet the geneticists, whose work seems to be connected very potentially in a significant manner, were unaware of that advance for that—whether it is an advance or not is a value judgment, but certainly that development.

Dr. SLOAN. I think they were unaware because in general they felt that we were still in the data-gathering stage, and were not expecting that people would turn this data-gathering technique——

Mr. SHAMANSKY. Now that you have raised the question in effect, do you feel an obligation on the part of the scientific community, the geneticists, to raise a warning sign saying, "You are getting beyond the valid data"?

Dr. SLOAN. I have written a letter to the president of the Society for Pediatric Research alerting him to this, and I am hoping that we will take this up at our next meeting, since the greatest concentration of human geneticists are in that society and in the American Society of Human Genetics, of which I am also a member. I have alerted both of these groups to this development, and hope that we will discuss it at our next meeting.

Mr. SHAMANSKY. Could you tell us what scientific body, quasi-governmental, governmental, private, that you would direct this information toward? Who would you tell? Who is out there listening? How do you get the message, good or bad?

Dr. SLOAN. I think the American Society of Human Genetics, the Society for Pediatric Research and probably the Society for Clinical Investigation are three of the major groups that would have most of the human geneticists in them. If you are asking me about a Government agency——

Mr. SHAMANSKY. I was thinking of the National Academy of Sciences.

Dr. SLOAN. The National Academy of Sciences would not be appropriate. I think they are so highly geared toward other activities.

Mr. SHAMANSKY. I hope you understand what I am driving at. I worry that there is a relatively small group, although very qualified, a small group that end up talking among themselves. In other words, I see the geneticists talking here and yet industry is moving along here and I want them to talk to each other.

Dr. SLOAN. I did not have the slightest knowledge this was going on until I heard Mr. Gore on the MacNeil-Lehrer Report. That was my initiation into this situation.

Mr. SHAMANSKY. There is something to be said for communication and an articulate spokesman for it.

Dr. SLOAN. I was totally unaware of the extent to which this had penetrated into the workplace.

Mr. SHAMANSKY. Are you satisfied with the response of the geneticists with respect to this problem—not problem—the situation?

Dr. SLOAN. I do not think there has been enough time to respond yet.

Mr. SHAMANSKY. Thank you very much, doctor.

Mr. GORE. Thank you.

Let me recognize counsel for the minority, Mr. Clement.

Mr. CLEMENT. Thank you, Mr. Chairman.

Dr. Sloan, I am somewhat concerned in that you seem to have made an intuitive leap earlier in the hearing, and I am not quite sure that I understand how it worked. The previous witness stated that he had conducted his experiments using white blood cells and he had irradiated them with X-ray radiation with 100 rads, which is a very heavy dose, about 1,000 times what an average chest X-ray would be. He then argued from that that the ability of the DNA molecules to repair themselves was predictive of the long-term ability of the body to fight off the consequences of that irradiation based on his observations. He then said that one-third of the population based on his study should not necessarily be exposed to radiation and toxic chemicals that could cause DNA damage, and that is a direct quote from his testimony.

My question really is to you as a researcher, can you actually correlate the ability of the DNA molecule to repair itself based on X-ray irradiation to exposure to a toxic chemical? Are they in fact the same?

Dr. SLOAN. That is about 10 questions in 1. I would say that first of all, the type of experiments you are talking about obviously cannot be done in humans. Being a member of our human subjects committee, I can assure you that that type of experiment would never be done in humans. Therefore, you are looking at animal experiments, and animals may respond quite differently from humans.

You have problems—there surely are certain chemical agents which exert effects analogous to radiation; there are others which exert their toxic effects in totally different ways. So I do not think you can make a one-to-one correlation there. There are some chemical agents, for instance, the drugs used in fighting leukemia and certain types of cancer, that are alkylating agents and which have an effect not terribly dissimilar from radiation. Other drugs interfere with normal metabolic processes. We have a host of toxicological agents. You therefore need a battery of tests. No one test is going to tell you everything. I do not know how you can come up with a figure of one-third or one-fifth or any number.

I think some people are more susceptible to genetic breaks than others. This has not been established except in a few diseases. But with the exception of those very rare diseases, it is not clear that some people are more susceptible to the effects of genetic breaks,

than others or that such differences have any long-term implication. You run into the same problem I raised with the asthma drug. You can have a finding which is statistically significant but not clinically significant—very dangerous water to tread on.

Mr. CLEMENT. Do we run into a problem of trying to extrapolate test results based on the fact that not only are the disease mechanisms not fully understood, but there is a long latency period?

Dr. SLOAN. Absolutely. That is why I gave the analogy to my field. Here we have a field that is, to my way of thinking, simple by comparison to the effects of environmental toxins. We know whether the patient is going to get the illness within a matter of weeks or months. We know whether the technique used is right. We do not have that latency period.

We have enough trouble as is. We were fooled for a long time—the FDA, for example, at one time mandated that all vaccines should be grown in a certain tissue culture cell line. Then they discovered that cell line was not that cell line anymore, it had changed. A cell line that had been growing in glass bottles and which people had been studying for years and years was wrong. A cell line that had been presumably checked each day had changed, and therefore the rules had to be changed. When we are dealing with a human being, the latency period may be 10, 20, or 30 years—I submit that we have a very tough problem to extrapolate from laboratory tests to clinical damage.

Mr. CLEMENT. A final question, Dr. Sloan, if you would. It seemed fairly obvious that in the test that was discussed earlier where you are working at very high levels of radiation or exposure that it is reasonably easy to determine what the results are in the DNA breaks and the ability to repair itself. However, 100 rads is considerably higher than a worker would normally be exposed to in the workplace. If you take it down to below the occupational standards, you are working at extraordinarily low levels in comparison. How do we filter out the background noise, whether it is radiation or whether it is exposure to chemical agents, not only in the workplace but in society, and take that part out so that if we do have a test that is reasonably predictive we can tell how much of the risk comes from the workplace and how much comes from ambient environmental exposure?

Dr. SLOAN. That is a wonderful question. It goes way beyond my expertise. I could give you names of people to talk to, but I am not competent to answer that question. It is a tough problem, and we all know it is a tough problem.

Mr. CLEMENT. But based on that, you would say that the state of the art is such that the tests that we have now just are not predictive enough to be countervailing?

Dr. SLOAN. One may well turn out to be predictive. We do not know which one is developed to that point.

Mr. CLEMENT. Thank you, Mr. Chairman.

Mr. GORE. Thank you.

Mr. Shamansky.

Mr. SHAMANSKY. Thank you, Mr. Chairman.

Dr. Sloan, it is interesting—the different facets of this problem that we are investigating. One is purely scientific, and others are legal and ethical. I would like to ask your opinion. Do you feel that

there is sufficient scientific predictability, given all the problems, you know, the cautions that you have advanced, to raise nevertheless ethical and legal questions; in other words, is there enough now for the ethicist and/or the lawyers or the lawmakers, as the case may be, to begin to respond?

Dr. SLOAN. I do not know if you can respond with legislation, but you would be well advised to respond with investigation. And I think it is incumbent upon you to start to gather the information. I have tried to indicate that I am dubious that we can make a connection between the laboratory test and what the results mean to the individual. But there surely are certain areas—one you and I talked about on the plane—there is a company that tests their employees who spray people's gardens and lawns with insecticides. The company monitors the level of the enzyme which is damaged by this insecticide. When the level reaches a certain level, the company will not allow the employee to spray insecticides for several weeks. There are two ways to look at that approach. The company is protecting their employees and themselves, but might they not be wiser to protect the employee from the agent to begin with?

Mr. SHAMANSKY. Of the various approaches, one would be a cost-effective, assumption of the risk, getting into the traditional legal and commercial responses, but whatever the company is doing, it is a rational response. At least it is not ignoring the problem.

Dr. SLOAN. It is a rational response for them to want to do it. I am not sure that it is proper for them to use that approach. You may have to stay their hand to prevent them from inflicting economic hardship where it is not justified on the basis of scientific data. That is my prejudice at this point. It is not scientifically proven, and until there is good, solid evidence, I would think that the burden rests primarily on the employer to make the workplace safe for everyone. We do not know whether, for instance, cells in culture, even in short-term culture, are precisely representative of cells in the intact human. As soon as one takes tissue out of the body, I do not care whether it is for 1 minute in culture or 20 days, the cells change. I am not certain you can be sure that a short-term exposure to a toxin will produce results in any way similar to those resulting from 10 days of exposure.

Mr. SHAMANSKY. The practical one is our company that we are talking about here. Do you consider it, as a matter of principle which should be unwavering, that you eliminate the factor to which the employee should not be exposed, or is it fair to weigh, say, the wearing of, say, a mask, or is there a cost-effective—can you ethically consider the whole question of cost-effectiveness?

Dr. SLOAN. I think it depends on the agent and it depends on the test. As we learn more, there will be some examples in which the evidence will initially be so overwhelming that society had better be careful. There will be many others in which the direction in which to proceed will be very unclear.

Mr. SHAMANSKY. So, as a matter of principle, you do not eliminate the issue of cost-effectiveness. You are open to saying in one case it might be appropriate; in another case, you eliminate the element rather than put on the mask?

Dr. SLOAN. If we find that most people who work with a certain agent do well while one small group of people with some identifi-

able characteristic keep on dying, then it behooves us to pay attention to that finding.

Mr. SHAMANSKY. But you could respond to that in various ways.

Dr. SLOAN. Right, by getting them out or by making the workplace safer

Mr. SHAMANSKY. Thank you, Doctor.

Mr. GORE. We have found that there are laws currently on the books which could be applicable to the kind of concerns that you raised in the case of the company that has employees spraying insecticide on lawns. If the test they are using to take people off the job is not accurate, OTA found that the current OSHA law would probably provide authority to the Administrator of OSHA to prescribe guidelines as to what kinds of tests are fair and what kinds of tests are unfair to the employees in circumstances like that, and it may be that we can come up with some legislative language on the OSHA act when it is before the Congress and some selective amendments on other statutes to take care of some of the worst of these potential problems.

It seems to me that the reason why you and other scientists have been surprised at the speed with which industry is picking up some of these techniques and looking for ways to use them may be that there has been an enormous upsurge in the legal pressures on industry to avoid occupational illness. You look at the stories in this morning's paper about the Manville Corp., for example, the latest wrinkles in its bankruptcy filing as a result of asbestos exposure, and the pressure is clearly present and growing. I appreciate the way you treat the issue, and the subcommittee appreciated your letter to the subcommittee in the wake of the last hearings, and I found your testimony extremely helpful and enlightening. So thank you very much for coming today. We appreciate it.

Mr. GORE. Our final witnesses will appear as a panel, Dr. Thomas Murray with the Institute of Society Ethics and Life Sciences at the Hastings Center, Hastings-on-Hudson, N.Y., and Mr. Alexander Capron, executive director of the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research.

We are delighted to have both of you here. You have both been leaders in the effort to apply ethical considerations to these frontier areas of science.

Dr. Murray, if you would lead off, we would appreciate it. Welcome.

STATEMENTS OF THOMAS MURRAY, PH. D., INSTITUTE OF SOCIETY ETHICS AND LIFE SCIENCES, HASTINGS CENTER, HASTINGS-ON-HUDSON, N.Y., AND ALEXANDER CAPRON, EXECUTIVE DIRECTOR, PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH

Mr. MURRAY. I would be happy to. Thank you for the invitation to appear before the committee.

I am going to be speaking exclusively about genetic screening. I am talking about tests used to detect preexisting conditions, inherited genetic conditions, with the intention to identify people who

are especially susceptible to one or another hazard in the workplace.

There are at least four general purposes possible for tests of this sort: clinical diagnosis, research, information, and exclusion. First, in diagnosis, the tests could be used to clinically diagnose an individual ill worker. Second, the test could be used in research to establish links between genetic predispositions and reactions to workplace hazards. Third, information gained from the tests along with any established or reasonably suspected link with work-related illness could be presented to workers for their consideration and possible action. Fourth, the tests could be used to exclude workers from jobs where they had a genetic condition believed to result in a heightened susceptibility to hazards normally encountered in that job.

Only the fourth of these potential uses raises the problem of coercion in a powerful way. Using genetic screening to exclude workers from jobs would create profound moral dilemmas, but it is not the only ethical problem in workplace genetic screening. In the other three categories of use, diagnosis, research, and information, there are also ethical considerations deserving our attention.

In every case, the ethical questions are complicated by the fact that we are focusing on the person's genetic makeup. This means several things. Our genetic makeup is fixed, unchangeable, and unchosen. It is also inherited along racial and ethnic lines. It is out of our control, and all the more frightening because of that. It raises at times the specter of racial discrimination.

Put another way, genetic tests are nakedly antiegalitarian.

The lesson of this is not, I think, that genetic testing is therefore undemocratic or morally wrong. I can imagine circumstances where it would be politically irresponsible and morally corrupt not to act on our knowledge of genetic differences. But facts about genetic makeups and predispositions are just that—facts—and we would be foolish to ignore them. Our political and moral problems begin when we ask what should we do about those facts. In its appeal to unchangeable and unchosen causes, genetic testing is unlike most other scientific or medical tools and social policies for eliminating workplace illness. Genetic differences are real; but so is the threat to our egalitarian ideal posed by an overreliance on genetic sorting of individuals into categories of susceptibility.

With that as prelude, I want to turn to the four purposes I mentioned earlier. Genetic anomalies are a possible factor in the etiology of disease for a particular sick person, whether that person be a worker or nonworker. It would be foolish to ban consideration of genetic factors in workplace-related disease when they might at times be significant contributing factors.

One problem raised in previous uses of genetic testing is a likely one in this context: misunderstanding the consequences of having a genetic abnormality. Fortunately, the misunderstanding problem is solvable. Good medical practice generally requires that physicians explain to their clients just what significance a finding of a particular genetic abnormality has. Rarely will the news be as catastrophic as people might fear. Unfortunately, good medical genetic counseling is probably less common than it should be, and individuals are and will be misinformed and uninformed. Still, I see no compel-

ling reason for interfering with a physician's use of genetic tests to uncover the etiology of illness in specific ill workers, but that is not genetic screening as it is usually understood. That is genetic testing for diagnosis.

The second major purpose for genetic testing in the workplace is for research. This category is especially important since, as I understand the scientific evidence and as the testimony has confirmed, there is as yet no firm evidence to support using genetic screening to select among potental workers according to their susceptibility to hazards. Even in cases where we have sound theoretical reasons for believing a connection exists between genetic conditions, workplace exposures, and illness, at least two of the final three pieces of the puzzle are missing. Piece No. 1 is individual clinical reports suggesting that workers with that particular condition are in fact getting sick. Piece No. 2 is epidemiological research confirming the link between populations of workers, workplace exposures, and illnesses. Piece No. 3 is feasibility studies showing that under the actual conditions of testing, workplace exposure, and such, using genetic screening does indeed reduce illness. For a handful of genetic factors we have the beginnings of piece No. 1. To my knowledge, we lack pieces 2 and 3 in every instance.

If we are to pursue the possibility of work-related genetic screening we need epidemiological research now and later, feasibility studies. In short, what we might do now is in other contexts called research with human subjects. People have struggled with the ethics of human subjects research for a number of years, and have reached a degree of consensus on many of the most basic issues, especially the importance of informed consent and of confidentiality. We have not decided whether and in what form these requirements should operate when the researchers are agents of the employer, when the subjects are also employees, and when the research's purpose may or may not benefit that particular population of workers.

How far to push the analogy between human subjects research outside the employment context and research done within a company on occupational illness is a complex question. I believe it deserves more attention. Since research is undoubtedly the most appropriate use of genetic screening in the workplace today, we should give thought to the duties and responsibilities of employers, researchers, and employee subjects.

My impression of the ethics of occupational health research done within companies is that we are roughly at the stage of most research with human subjects of 20 years ago—dependent on the judgment and integrity of the researcher. Whether or not subjects are asked for their consent for the research, whether or not they are informed of the purposes of it, whether or not the results of the participation are kept confidential, all these ultimately rely on the choice of the investigator or his or her supervisors. Whether this is satisfactory or not, I cannot say. I do think the issue is ripe for a candid public discussion. We have decided outside the workplace that more stringent protections are justified.

Other problems raised by research include what should be done with the knowledge gained, with whom should it be shared, and how do we deal with uncertainty. Once we are convinced that there is a connection between an anomaly, an exposure, and a disease, do

we have a duty to inform persons who may be at increased risk? How much certainty is appropriate before we warn people? Now, we have dealt with some of these questions. I will not say we have solved them. We have dealt with them in other arenas.

The third purpose of genetic screening in the workplace would be to present employees and prospective employees with information that might be pertinent to their decision to accept the job. Without scientific evidence linking their particular genetic anomaly to exposure and illness or without enough clinical evidence to suggest such a connection, it is difficult to see what result such a program would have. Using screening for information and choice assumes a factual base. If the factual base is weak or nonexistent, screening may serve other purposes, but not informed choice about job-related health risks.

If and when a scientific base is created, then sceening for information and choice strongly resembles population screening programs. Pesons who are identified as anomalous are given that information in order to make better-informed decisions on relevant matters. Screening newborns for PKU is one such program. Once identified, children at risk can be given a special diet which will save them from the worst ravages of the disease. While there are problems with the PKU screening programs, most observers acknowledge that it serves a useful social purpose. Early attempts to screen black populations for sickle cell trait are much more problematic. People often confused the disease with the trait. Many people were left with the misapprehension that they had the disease, which is unmistakable, and is also quite severe, with the trait, which may have no symptoms and be of no clinical relevance whatsoever and you need no test to tell you that you have the disease. The only decisions which could be influenced by the knowledge that one had the trait and not the disease were whom to marry, whether or not to have children, and whether or not to use amniocentesis and abortion if a child were conceived.

Undertaking a screening program confers an obligation to explain thoroughly what the genetic anomalies mean for one's life choices. Also the social desirability of the screening program depends very heavily on the decision choices which will be faced once you confirm the anomaly. At the least we should determine that the choices available are conscionable and we should offer an intensive and careful counseling program to explain the results of the test to each individual.

The most attention-grabbing potential use of genetic screening in the workplace is to identify workers with heightened susceptibility to particular hazards. Clearly this has no justification without strong scientific evidence confirming the connections between the specific anomalies, the exposures, and diseases. If and when we have such evidence it is still not obvious that exclusion from jobs is the best social policy or the most moral thing to do.

Let me set some boundaries. On the one hand imagine a condition which increases many times a person's likelihood of having cancer to 1 in 5 from a particular exposure, that there are only very few individuals with this, that there is an accurate and cheap test to identify it, and that the exposure is found in only a handful of jobs. I would hesitate to say that those workers who now have a

20-percent chance of cancer should be given those jobs—I think it is very unlikely they would want to have them. On the other hand, if many people have a condition, if it increases the relative and absolute risk by a small amount, if it involves substances found in hundreds of thousands of jobs, then I cannot see how to justify denying those jobs to those people. The practical wisdom and the ethics of exclusion from jobs for genetic factors will depend on several practical questions. Here is a partial list.

First of all, how many people have the anomaly.

This cuts two ways. The more people who have it, the more who will be affected by an exclusionary policy. The fewer who have it, the less cost-effective the screening program becomes, and the greater the ratio of false positives to true positives. You might misidentify a lot of people who did not have the trait as having it.

What is the relative risk for people with the anomaly for that substance? What is the absolute risk? Relative risk means their enhanced risk over and above the average person. Absolute risk means the actual chance that they are going to get the disease. If it is a very rare disease, they may have a fivefold increase in risk and a 1 in 20,000 chance of getting the disease.

How many people will be misidentified by a screening program? How many false positives and false negatives will there be?

If proportionately large numbers of people without the anomaly are falsely identified as having it, much confusion and mischief may result. This is lessened if you have a reliable followup to eliminate those initial false positives. If the number of people who actually have the anomaly but are missed in the screening is high, then its value as an exclusionary test is lessened considerably, and a negative finding may give people a false assurance when they are actually at high risk.

How many jobs are involved?

If there are very few jobs, then individuals' choices are not severely constrained. If many jobs are involved, particularly in industries which tend to dominate particular job markets, say a mining concern, constraints could be substantial and painful to those workers.

What is the character of the illness or illnesses in question? How serious are these diseases? Are they irreversible?

One would feel differently about a cancer with a long latency, a deadly cancer than a disease detectable in a preclinical stage? Are they contestable, that is, is their cause likely to be held in dispute?

Diseases that are fatal, irreversible, and undetectable in the early stages are the most troublesome.

How solid is the evidence linking specific genetic conditions, with specific workplace substances at exposure levels likely to be found in the contemporary workplace, to actual diseases?

The more speculative the scientific base, the less exclusionary policies are warranted.

Does the screening program concentrate on groups with a history of having suffered discrimination?

It is in the nature of genetic traits to fall along racial lines. When the trait in question occurs disproportionately often among members of an historically mistreated group, there is likely to be a feeling that this is just another obstacle placed in the way of fair

and equal treatment. We should scrutinize with great care any exclusionary screening program having a focus or disproportionate impact on such groups.

How does genetic screening compare in its cost-effectiveness to other programs that would reduce work-related disease?

I have heard the fear expressed that screening might be used as an alternative to cleaning up workplaces. Whether or not this is true, screening should not be seen as a magical solution to the problem of occupational disease. It is simply one possible strategy among many, with economic costs but also human costs and benefits. We should not want to limit our decision to economic considerations.

We should remain aware that a policy of genetic screening and exclusion meshes very poorly with our egalitarian and meritocratic ideals. Using such a policy will incur significant moral and political costs, costs not attaching to other policy options.

Let me offer six tentative conclusions.

First, using genetic tests to diagnose specific illnesses in individual workers is generally acceptable. It does confer a duty on the physician to explain fully and in terms comprehensible to that person what having a genetic condition does and does not mean.

Second, research on the relation between genetic anomalies, workplace exposures, and disease is a defensible activity at this time. However, we need a candid public discussion about the extent to which our moral and legal rules governing human experimentation in other areas should apply to this type of research, a discussion I have not heard up to now.

Third, informing workers about their genetic anomalies becomes justifiable when good evidence linking anomaly, exposure, and disease appears. Until then, such information can serve other purposes, but not the one of permitting an informed assumption or refusal of risks. In any case, employers have a duty to anticipate and dispel misconceptions about the significance of genetic abnormalities.

Fourth, a morally defensible exclusion policy has one absolute requirement and several conditional ones. There must be a sound scientific basis linking anomaly to exposure to disease. I hate to be repetitive, but that point must be made. Relative and absolute risks should be very large. Misclassifications should be few and reversible. The number of persons excluded should be very small. Very few jobs should be involved. The disease should be severe, irreversible, and not readily diagnosed in the preclinical phases. It should not single out already beleaguered groups.

Fifth, the moral and political costs associated with exclusionary policies based on genetic criteria ought to be weighed heavily when considering what mix of policies will most efficiently and fairly protect the health of workers without imposing unsustainable costs on employers and the public. In general, policies should follow the least restrictive alternative principle.

Sixth, whatever else we learn, we must recognize that our choices here are not dictated by scientific or economic considerations. They are influenced, certainly, but determined, clearly not. The choices we face are political and moral: How to protect the interests of society and the health of workers without unduly inter-

fering with personal liberty and while preserving a good measure of social justice.

On behalf of the Hastings Center I want to thank you for your attention to the ethical issues here.

Mr. GORE. Thank you for extremely thoughtful, well-prepared testimony. We appreciate it.

[The prepared statement of Thomas H. Murray follows:]

Statement of

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GENETIC SCREENING IN THE WORKPLACE: ETHICAL ISSUES

Any discussion of the ethical issues in using tests for heritable genetic traits in the workplace must begin by acknowledging that the ethical problems and their resolutions will depend in part upon the purposes for which the tests are used. There are at least four general purposes possible: diagnosis, research, information, and exclusion. First, the tests could be used in the clinical diagnosis of an individual ill worker. Second, tests could be used in research to establish links between genetic predispositions and reactions to workplace hazards. Third, information gained from the tests, along with any established or reasonably suspected link with work-related illness, could be presented to workers for their consideration. Fourth, the tests could be used to exclude workers from jobs where they had a genetic condition believed to result in a heightened susceptiblity to the hazards normally encountered in that job.

Only the fourth of these potential uses raises the problem of coercion in a powerful way. My reading of the literature raising moral objections to workplace screening strongly suggests that this potentially coercive use of genetic screening is what most observers fix upon, and which is morally most objectionable. I agree that using genetic screening to exclude workers would create profound moral dilemmas. But it is not the only ethical problem in workplace genetic screening; in the other three categories of use--diagnosis, research, information--there are also ethical considerations that deserve our attention.

In every case, the ethical questions are complicated by the fact that we are focusing on a person's genetic makeup. This means several things.

Our genetic makeup is fixed, unchangeable, unchosen. It is also inherited along racial and ethnic lines. It is out of our control--and all the more frightening because of that. Finally, it raises the specter of racial discrimination.

Putting it another way, genetic tests are nakedly antiegalitarian. Just the opposite of the proposition that all persons are created equal, homing in on our genes emphasizes the absolutely fundamental differences among people. Our meritocratic ideal at least allows for effort to overcome discrepancies in natural talent. Going right to the genes does not permit even that.

The lesson of this is not, I think, that genetic testing is therefore undemocratic or morally wrong. I can imagine circumstances where it would be politically irresponsible and morally corrupt not to act on our knowledge of genetic differences. But, facts about genetic makeups and predispositions are just that--facts--and we would be fools to ignore them. Our political and moral problems begin when we ask what should we do about those facts. In its appeal to unchangeable and unchosen causes, genetic testing is unlike most other scientific or medical tools and social policies for limiting workplace illness. Genetic differences are real; so is the threat to our egalitarian ideal posed by an overreliance on genetic sorting of individuals into categories of susceptibility.

Diagnosis

With that as prelude, I want to turn to the four purposes I mentioned earlier. First, genetic anomalies are one possible factor in the etiology of disease for a sick person--worker or non-worker. It would be foolish to ban consideration of genetic factors in workplace-related disease when

they might be significant contributing factors. But we should be wary of its potential misuses. We used to say that someone who developed coughing spasms and breathing difficulties had "weak lungs"; now we might say that she has SAT deficiency. It may be true; it may not. The danger is that we lay the cause on the person and exonerate the environmental or workplace conditions which precipitated the disease. The fact that an individual developed that specific disease under those particular conditions merely reflects the undeniable truth of the statement that all disease depends on the interaction of organism and environment. Which of the two we focus on is a social and political choice with important ethical consequences.

In addition to this form of victim-blaming, diagnosing an illness as genetically caused may label that individual as constitutionally weak, and make it difficult to find another job, should the original one be lost, and generally cause others to respond to the person in an unjustified manner.

Whether or not either of the first two adverse consequences occurs, there is a third which in light of our previous experience with genetic screening is very likely: misunderstanding the consequences of having a genetic abnormality. Fortunately, the misunderstanding problem is solvable: good medical practice generally requires that physicians explain to their clients, in language those people can comprehend, just what significance a finding of genetic abnormality has. Rarely will the news be as catastrophic as the lay imagination might fear. Unfortunately, good medical genetic counseling is probably less common than it should be, and individuals are and will be misinformed and uninformed. Still, I see no compelling reason or practical basis for interfering with the physician's use of genetic tests to uncover the etiology of illness in specific, sick workers.

Research

The second major purpose for genetic testing in the workplace, and, specifically, large scale testing (as implied in the term "screening") is for research. This category is especially important since, as I understand the scientific evidence, there is as yet no firm evidence to support using genetic screening to select among potential workers according to their susceptibility to hazards. Even in the cases where we have sound theoretical reasons for believing a connection exists between genetic conditions, workplace exposure, and illness, at least two of the three final pieces of the puzzle are missing. Piece number 1 is individual clinical reports suggesting that workers with the genetic condition are indeed getting sick. Piece number 2 is epidemiological research confirming the link between populations of workers, workplace exposures, and illness. Piece number 3 is feasibility studies showing that, under the actual conditions of testing, workplace exposure, and such, using genetic screening does indeed reduce illness. For perhaps a handful of genetic factors, we have the beginnings of piece number 1. To my knowledge, we lack pieces 2 and 3 in every instance.

If we are to pursue the possibility of work-related genetic screening, our most pressing need now is for epidemiological research, and later, if appropriate, feasibility and outcome studies. In short, what we might do now is in other contexts called research with human subjects. We have struggled with the ethics of human subjects research for a number of years, and have reached a degree of consensus on the most basic issues, especially the importance of informed consent, and of confidentiality. What we have not decided is whether and in what form these requirements should operate when the researchers are agents of the employer, when the subjects are also employees, and when the research's purpose may or may not be to benefit that particular population of workers.

I do not believe the issue of research within companies has received much attention so far, with the possible exception of new drug testing done by pharmaceutical companies using their own employees as subjects. That, however, is a special case--product development--and not analogous to the one at hand--research on occupationally related disease. How far to push the analogy between human subjects research outside the context of employment, and research done within a company on occupational illness is a complex question. I believe it deserves more attention, especially to its legal and moral dimensions. Since research is probably the most appropriate use of genetic screening in the workplace today, we should give serious thought to the duties and responsibilities of employers, researchers, and employee-subjects.

My impression of the ethics of occupational health research done within companies is that we are at roughly the stage of most research with human subjects 20 years ago--dependent on the judgment and integrity of the researcher. Whether or not subjects are asked for their consent, whether or not they are informed of the purposes of the research or even of the fact that research is taking place, whether or not the results of their participation are kept confidential, ultimately rely on the choice of the investigator or his or her superiors. Whether this is satisfactory or not, I cannot say; I do think that the issue is ripe for a candid public discussion.

Other problems raised by research are: What should be done with the knowledge gained? With whom should it be shared? And how do we deal with uncertainty? Once we become reasonably convinced that there is in fact a connection between an anomaly, an exposure, and a disease, do we have a duty to inform persons who we now realize may be at enhanced risk? How much certainty is appropriate before we warn individuals? Before we disseminate our findings informally, or formally through publication? Many of these questions have clear analogies in other kinds of human subjects research.

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Information

The third purpose of genetic screening in the workplace would be to present employees and prospective employees with information that might be pertinent to their decision to accept a job. Without scientific evidence linking their particular genetic anomaly to exposure and illness, or at least enough clinical evidence to strongly suggest such a connection, it is difficult to see what constructive use such a screening program might have. In short, using screening for information and choice assumes a factual base; if the factual base is weak or nonexistent, screening may serve other purposes, but not informed choice about job-related health risks.

If and when a scientific base is created, then screening for information and choice strongly resembles population screening programs. Persons who are identified as anomalous are given that information, in order to make better informed decisions on relevant matters. Screening newborns for PKU is one such program. Once identified, children at risk can be given a special diet which will save them from the worst ravages of the disease. While there are problems with the PKU screening programs, most observers acknowledge that they have served a useful social purpose. Early attempts to screen populations of blacks for sickle-cell trait were more problematic. People often confused the disease with the trait, and the screeners did not always do what was necessary to dispel that confusion. Many people were left with the misapprehension that they had the homozygous disease rather than the heterozygous trait. Furthermore, about the only decisions which could be influenced by the knowledge that one had the trait (you did not need a genetic test to know you had the diease) were whom to marry, and whether or not to have children, or use amniocentesis and abortion if a child were conceived.

My point is twofold: that undertaking a screening program confers an obligation to explain thoroughly just what the genetic anomalies mean for one's life choices; and that the social desirability of a screening program depends heavily on the decision choices which will be faced once an anomaly is confirmed. At the least, we should determine that the choices available are conscionable. And we should offer an intensive and careful counseling program to explain the results of the tests for each individual.

Exclusion

The most attention-grabbing potential use of genetic screening in the workplace is to identify workers with heightened susceptibility to particular hazards. Clearly, this has no justification without strong scientific evidence confirming the connections between the specific anomalies, exposures, and diseases. If and when we have such evidence, it is still not obvious that exclusion from jobs is the best social policy or the most moral thing to do.

Let me set some boundaries. On the one hand, if very few people have the condition, which increases their likelihood of developing cancer from exposure to some substance found in only a handful of jobs several hundredfold to a probability of one in five, then I would have little hesitation in saying that they should not be permitted to take one of these jobs, even in the unlikely case that they would want to. On the other hand, if many people have the condition, if it increases their relative and absolute risks by only a minute amount, if it involves substances found in hundreds of thousands of jobs, then I cannot justify denying those jobs to those people. The practical wisdom--and the ethics--of exclusion from jobs for genetic factors will largely depend on several practical questions. I will mention

those issues I believe are relevant. This should be regarded as a partial list, to be completed by others--scientists and experts in our legal and political traditions, to name two.

Questions underlying an ethical analysis of screening leading to exclusion.

1. How many people have the anomaly?

This cuts two ways. The more people who have it, the more who will be affected by a policy of exclusion. The fewer people who have it, the less cost-effective a screening program becomes, and the greater the ratio of false positives to true positives.

2. What is the relative risk for people with the anomaly for that substance? What is the absolute risk?

Small increases in relative risk do not justify exclusion. Even with large increases in relative risk, if the absolute risk remains low, exclusion is hard to justify.

3. How many people will be misidentified by a screening program? How many false positives will there be? How many false negatives?

If proportionately large numbersof people without the anomaly are falsely identified as having it, then much confusion and mischief may be done. This is lessened if reliable follow-up tests can eliminate the initial false positives. If the number of people who actually have the anomaly but are missed in the screening--false negatives--is high, then its value as an exclusionary test is lessened considerably, and a negative finding may constitute a false assurance to people who are at heightened risk.

4. How many jobs are involved?

If very few jobs would be subject to exclusion, then individuals' choices are not severely constrained. If many jobs are involved, particularly in industries which tend to dominate particular job markets, then the constraints may be substantial.

5. What is the character of the ilness or illnesses in question? How serious are they? Are they irreversible? Are they detectable at a pre-clinical stage? Are they contestable, that is, is their cause likely to be in dispute?

Clearly, diseases that are fatal, irreversible, and undetectable in early stages are more troublesome, and better justify paternalistic interventions to protect workers even when they might prefer not to be protected.

6. How solid is the evidence linking specific genetic conditions with specific workplace substances at exposure levels likely to be found in the contemporary workplace to diseases?

The more speculative the scientific base, the less exclusionary policies are warranted.

7. Does the screening program concentrate on groups with a history of having suffered discrimination?

It is in the nature of genetic traits to fall along racial lines. When the trait in question occurs disproportionately often among members of an historically mistreated group, there is likely to be suspicion and mistrust on the one hand, and a feeling that this is just one more obstacle placed in the way of fair and equal treatment. We should scrutinize with great care any exclusionary screening program having a focus or disproportionate impact on such groups.

8. How does genetic screening compare in its cost-effectiveness to other programs that would reduce work-related disease?

I have heard the fear expressed that screening might be used as an alternative to cleaning up workplaces. Whether or not this is true, screening should not be seen as a magical solution to the problem of occupational disease. It is one possible strategy among many, with its own economic and human benefits and costs.

We should remain aware that a policy of genetic screening and exclusion meshes very poorly with our egalitarian and meritocratic ideals. Using such a policy will incur significant moral and political costs--costs not attaching to other policy options, for example, lowering exposures for all workers.

With some trepidation, I offer six tentative conclusions.

I. Using genetic tests to diagnose specific illnesses in individual workers is generally acceptable. It does confer a duty on the physician to explain fully and in terms comprehensible to the person what having that genetic condition does and does not mean for that individual.

II. Research on the relation between genetic anomalies, workplace exposures, and disease is a defensible activity at this time. However, we need a candid public discussion about the extent to which our moral and legal rules governing human experimentation in other arenas should apply to this type of research.

III. Informing workers about their genetic anomalies becomes justifiable when good evidence linking anomaly, exposure, and disease appears. Until then, such information can serve other purposes, but not the one of permitting an informed assumption or refusal of risks. In any case, employers have a duty to anticipate and dispel misconceptions about the significance of genetic abnormalities.

IV. A morally defensible exclusion policy has one absolute requirement and several conditional ones:

a. There must be a sound scientific basis linking anomaly to exposure to disease;

b. relative and absolute risks should be very large;

c. misclassifications should be few and reversible;

d. the number of persons excluded should be very small;

e. very few jobs should be involved;

f. the disease should be severe, irreversible, and not readily diagnosed in its pre-clinical phases;

g. it should not single out already-beleaguered groups.

V. The moral and political costs associated with exclusionary policies based on genetic criteria ought to be weighed heavily when considering what mix of policies will most efficiently and fairly protect the health of workers, without imposing unsustainable costs on employers and the public. In general, policies should follow the "least restrictive alternative" principle.

VI. Whatever else we learn, we must recognize that our choices here are not dictated by scientific or economic considerations; influenced, certainly, but determined, clearly not. The choices we face are political and moral: How to protect the interests of society and the health of workers without unduly interfering with personal liberty and while preserving a good measure of social justice.

Mr. GORE. We will hold questions until Mr. Capron completes his statement. I would like to give a special welcome to Mr. Capron. We have enjoyed the opportunity to work with you, Mr. Capron, and look forward to your presence at a later set of hearings in mid-November on gene therapy and human genetic engineering. And on this occasion, let me congratulate you again on the fine work that your Commission has done and is doing, and it is really a great benefit to our society.

Without objection, your entire statement will be put in the record, and we will invite you to proceed with the presentation.

Mr. CAPRON. Thank you. Let me therefore abbreviate what I have to say.

You have asked me to speak concerning the work of the President's Commission on the ethical and legal implications of genetic screening and counseling. Since this study is not yet complete, my comments are based on the Commission's tentative but not yet final conclusions. Indeed, the Commission will be meeting and considering a draft report on this subject at its meeting on Friday and Saturday this week.

The Commission focused its attention on genetic screening undertaken for reproductive reasons and on screening for early detection of disease in a medical setting, since the Office of Technology Assessment was conducting the concurrent study of occupational screening. It seems important to me, especially in an oversight context, not artificially to separate these types of screening. The various reasons for screening and counseling or the settings in which they take place do not in themselves provide bases for the adoption of different policies toward participants. Not only will policies in one area have implications for the policies to be followed in another, but separating them could have particularly significant adverse consequences for the participants. For example, as I will argue in a few moments, it seems very important for screening of workers for genetic susceptibility to be done in a way that will provide the persons screened with benefits and that it is integrated into their general health care. That good is undermined if occupational screening is segregated conceptually from other genetics programs and services. Therefore, I hope it will be helpful for me to share with you some observations drawn from the Commission's work as it seems to relate to occupational genetic testing. And I, too, will address myself to what you have termed true genetic screening rather than monitoring for mutagenicity.

The analysis and conclusions that might be drawn from the Commission's work fall into several categories. They are tied together, however, by two common threads. First, we have been struck by the enormous benefits that genetic services can offer people. In focusing on safeguards or limits, no implication is intended that a great deal of knowledge will not be produced of benefit to the participants. Second, decisions about such programs, although they must rest on a sound scientific and economic analysis, are also ethical choices, meaning that aids to decisionmaking—such as cost-benefit analysis, when permissible—fall far short of answering all the difficult questions that must be addressed about the distribution of risks and benefits created by any program. Therefore, it is important for those making decisions about programs, whether

they be individual patients, geneticists, and other health care providers, or public administrators and legislators, to be aware of the choices that must be made.

For the record, I am submitting a copy of the draft conclusions of the Commission that address five areas in which the operation of genetics programs have ethical and legal implications: Confidentiality, autonomy, knowledge, personal well-being, and equity. I would be pleased to elaborate on any of those conclusions, but in order to keep this opening statement brief I will just highlight a couple of points.

Mr. GORE. Without objection we will hold the record open for the draft conclusions that you have reached, but perhaps it would be appropriate for us to hold the record open until the Commission has completed its final review, which if it is going to take place this weekend——

Mr. CAPRON. I would be pleased to have your record reflect the Commission's actual conclusions rather than this tentative version.

Mr. GORE. We will do that.

[The information follows:]

SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

The Commission's basic conclusion is that programs to provide genetic education, screening, and counseling provide valuable services when they are established with concrete goals and specific procedural guidelines founded on sound ethical and legal principles. The major conclusions fall into five categories.

A. Confidentiality

(1) Genetic information should not be given to unrelated third parties, such as insurers or employers, without the explicit and informed consent of the person screened or a surrogate for that person.

(2) Private and governmental agencies that use data banks for genetics-related information should require that stored information be coded whenever that is compatible with the purpose of the data bank.

(3) The requirements of confidentiality can be overriden and genetic information released to relatives (or their physicians) if and only if the following four conditions are met: (a) reasonable efforts to elicit voluntary consent to disclosure have failed; (b) there is a high probabilty both that harm will occur if the information is withheld and that the disclosed information will actually be used to avert harm; (c) the harm that identifiable individuals would suffer if the information is not disclosed would be serious; and (d) appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.

- When it is known in advance that the results of a proposed screening program could be uniquely helpful in preventing serious harm to the biologic relatives of individuals screened, it may be justifiable to make access to that program conditional upon prior agreement to disclose the results of the screening.

(4) Law reform bodies, working closely with professionals in medical genetics and organizations interested in adoption policies, should urge changes in adoption laws so that information about serious genetic risks can be conveyed to adoptees or their biological families. Genetic counselors should mediate the process by which adoptive records are unsealed and newly discovered health risks are communicated to affected parties.

B. Autonomy

(5) Mandatory genetic screening programs are only justified when voluntary testing proves inadequate to prevent serious harm to the defenseless, such as children, that could be avoided were screening performed. The goals of "a healthy gene pool" or a reduction in health costs cannot justify compulsory genetic screening.

(6) Genetic screening and counseling are medical procedures that may be chosen by an individual who desires information as an aid in making personal medical and reproductive choices.

- Professionals should generally promote and protect patient choices to undergo genetic screening and counseling, although the use of amniocentesis for gender selection should be discouraged.

- The value of the information provided by genetic screening and counseling would be diminished were available reproductive choices to be restricted. (This is a factual conclusion that is not intended to involve the Commission in the national debate over abortion).

C. Knowledge

(7) Disclosure of incidental findings (such as nonpaternity) or of sensitive findings (such as diagnosis of an XY-female) should begin with a presumption in favor of disclosure, while still protecting a client's other interests, as determined on an individual basis. In the case of nonpaternity, accurate information about the risk of the mother and putative father bearing an affected child should be provided even when a full disclosure is not made.

(8) Efforts to develop genetics curricula for elementary, secondary, and college settings and to work with educators to incorporate appropriate materials into the classroom are commendable and should be furthered. The knowledge imparted is not only important in itself but also promotes values of personal autonomy and informed public participation.

(9) Organizations such as the American Association of Medical Colleges, the American Medical Association, and the American Nursing Association should encourage the upgrading of genetics curricula for professional students. Professional educators, working with specialty societies and program planners, should identify effective methods to educate professionals about new screening tests. Programs to train health professionals, pastoral counselors, and others in technical, social, and ethical aspects of genetic screening deserve support.

D. Well-being

(10) A genetic history and, when appropriate, genetic screening should be required of men donating sperm for artificial insemination; professional medical associations should take the lead in identifying what genetic information should be obtained and in establishing criteria for excluding a potential donor.

- Records of sperm donors are necessary, but should be maintained in a way that preserves confidentiality to the greatest extent possible.

- Women undergoing artificial insemination should be given genetic information about the donor as part of the informed consent process.

(11) Screening programs should not be undertaken unless the results that are produced routinely can be relied upon.

- Screening programs should not be implemented until the test has first demonstrated its value in well-conducted, large-scale pilot studies.

- Government agencies involved in introducing new screening projects should require appropriate pilot studies as a prerequisite to approval of the product or to the funding of services.

- Government regulators, funding organizations, private industry, and medical researchers should meet to discuss their respective roles in ensuring that a prospective test is studied adequately before genetic screening programs are introduced.

(12) A full range of prescreening and follow-up services for the population to be screened should be available before a program is introduced.

- Community leaders and local organizations should play an integral part in planning community-based screening programs.

- States governments should consider establishing a review group with professional and public members to oversee genetic services.

- New screening programs should include an evaluation component.

E. Equity

(13) Access to screening may take account of the incidence of genetic disease in various racial or ethnic groups wtihin the population without violating principles of equity, justice, and fairness.

(14) When a genetic screening test has moved from a research to a service delivery setting, implicit or explicit policies limiting access to the genetic service should be subjected to review by a broadly based process that is responsive to the full range of relevant considerations, to changes in relevant facts over time, and to the needs of any groups excluded.

- The time has come for such a review of the common medical practice of limiting amniocentesis for "advanced maternal age" to women 35 years or older.

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(15) Determination of issues such as which groups are at high enough risk for screening or at what point the predictive value of a test is sufficiently high require ethical as well as technical analyses.

(16) Cost-benefit analysis can make a useful contribution to allocational decisionmaking, provided that the significant limitations of the method are clearly understood; it does not provide a means of avoiding difficult ethical judgments.

Mr. CAPRON. A couple of points.

First, experience with other genetics programs underlines the importance of careful research to arrive at a good understanding of the condition for which tests are being conducted as well as the specificity, sensitivity, and predictive power of the testing method prior to launching a testing program. Not only is it necessary to avoid premature implementation of a screening procedure, but the fact that the research relates to the workplace does not exempt it from usually accepted standards for all experimentation with human beings.

Twenty years ago the first mass genetic screening program was launched with the initial trials of the Guthrie inhibition assay for phenylketonuria [PKU]. By testing newborns, the screeners hoped to discover which babies needed a special diet intended to prevent the development of the mental retardation that is one consequence of PKU. The great enthusiasm for this test, which led rapidly to the adoption of mandatory screening laws in most States, obscured large gaps in understanding both of the disease and of the significance of certain test results. Fortunately, this did not result in major tragic consequences from the screening program, but the Commission found that many leading human geneticists today regard the experience with PKU as a reminder of the need to use greater care in the adoption of screening techniques for other genetic diseases.

I thought it would be helpful because of the questions that were raised if I were to explain some of the terms that you have heard today, and I will use a blackboard to do that if that is all right, and I think I can be heard.

Mr. GORE. I wonder if one of those microphones will reach over there. Let me ask the staff to see if that is possible.

Mr. CAPRON. The television will not pick that up, but they will not care that much.

Mr. GORE. It is C Span. Let me welcome them. They provide a great service. They provide this to cable television viewers coast to coast, and for the people who may be following it, if you could sort of speak toward that mike——

Mr. CAPRON. I stopped my prepared remarks at this point because it is particularly relevant regarding PKU screening. PKU, a disease which occurs in about 1 in 14,000 births, is called an inborn metabolism. It is one for which there is a treatment. It is representative of a great many genetic diseases that are very rare, and it is relevant to keep that in mind when we are talking about many forms of susceptibility screening. They will be looking for probably fairly rare conditions.

[Fig. 1 follows:]

FIGURE 1

NEWBORN SCREENING FOR PKU
BY INHIBITION ASSAY

Occurrence of Disorder*

Outcome of Screening Test	Present	Absent	Total Tested
Positive	1	19	20
Negative	0	13,980	13,980
TOTALS	1	13,999	14,000

Sensitivity = 100% (1/1 individuals actually affected are "positive" on screen)
Specificity = 99.99% (13,980/13,999 individuals actually unaffected are "negative" on screen)
Predictive value = 5% (1/20 reported "positives" are actually affected; the other 19 are "false positives")

* Assuming that PKU occurs once in 14,000 live births and that all babies are tested at an appropriate time after birth.

Say we are going to screen 14,000 newborns [fig. 1]. Now, the testing method can lead to a positive result or a negative result, and within any category, a positive result or negative result, there will be some who actually have the disease and some who do not have it. In PKU screening, as it turns out, if you get out of 14,000, 20 positive tests, 19 of those 20 will be false positives—that is, they will test as having the disease on the screen, but they do not have it. One will have it. That is the relative rate.

On the other hand, with present testing methods, if they are used at the appropriate age, at the level at which the test is now set, the prediction is that you will have no false negatives. One of the problems with PKU testing today is that it is used shortly before the baby leaves the hospital, and with increasingly early discharge of children from the hospital the level of phenylalanine in the blood may not have risen very much, so the test level is set quite low. There are indications of false negatives because of the way testing is done today, but the level on the screening assay that is used to say which are positive and which are negative, you should get no false negatives, therefore, we can assume that the other 13,980 negatives will test negative.

The term "sensitivity" here relates to how many of those who actually have the disease are found by the test to have the disease. So sensitivity here is 100 percent—1 child out of the 14,000 is picked up by a test. "Specificity" here will refer to those children who do not have the disease who are said not to have the disease, and again it is almost 100 percent, because the number who do not have it who are shown not to have it, are 13,980 out of 13,999. So it is very specific.

When we come to the predictive value of the test, however, we are looking at whether or not a positive test result indeed shows that the person has the disease. And here the predictive value of this test as you can see is only 5 percent.

What is the reason that the test yields such a low predictive value? The concern is when we are talking about a PKU test, we are talking about a figure that comes out on the test, and you will have an array of numbers. If that number were set at a lower level so that you picked up fewer of these false positives, you might occasionally miss a true positive. The effect of missing a positive is that the child could develop mental retardation, which would have been preventable with the dietary treatment when it is given at an early stage. If the existence of the PKU is not caught at that stage, it may not be caught until the child begins to develop signs, and then the doctor may not look for it because he thinks there was a screen and it came out negative. If you set the test lower, you may reduce the sensitivity of the test. We are talking about screening, and in most cases screening is thought of just what it sounds like. You catch certain things—like putting sand through a sieve, you are going to catch certain pebbles.

If you have another test which can differentiate those true positives from the false positives, no harm is done except for the cost of retesting, and the psychological trauma to the family during the period of uncertainty. There may be expense in terms of tests and there may be unhappiness, but it is not likely to have a major cost. I wanted to emphasize that is an ethical judgment. It is not some-

thing you can do on cost-benefit alone. You have to judge whether the harm to the people being falsely screened as having PKU and later found not to have it is greater than the harm that would occur by missing a few.

Let me shift this to an actual example from the workplace.

Mr. GORE. Before you do that, in terms of the example you have chosen, the remedy that avoids it is merely a change in diet?

Mr. CAPRON. The remedy that avoids the harm to the children who have PKU is the change in the diet. It is a restricted diet that lowers the level of phenylalanine. You would not want to give that diet to children who do not need it, because then they would be losing a protein that they need. But it is harmful to this rare child, 1 in 14,000.

Mr. GORE. The change in diet is prescribed for all 20?

Mr. CAPRON. No. Before the 20 are given the diet, they are tested. This is a screening technique that can be followed up with an accurate diagnostic technique. The screening technique is a very simple technique. Before the child leaves the hospital, there is a little pinprick on the heel, and a drop of blood is gathered on filter paper. The paper is sent to the laboratory, and the laboratory punches out circles of the filter paper and puts them on trays. [One way error sometimes occurs is if you get the wrong child with the wrong circle.] Then there is a biological technique that is used to see whether or not something grows in those different trays, and they will grow differently by the presence or absence of a high level of phenylalanine in the blood sample from a child.

Mr. GORE. So the screen picks up 20 possibles out of 14,000, and then a second test——

Mr. CAPRON. Which is more accurate, but which would be too expensive to do on all 14,000.

Mr. GORE. Then they isolate the one?

Mr. CAPRON. I am simplifying this. Obviously there are cases in which, as I said, some are missed occasionally. There are other cases in which you may need repeated testing. The child getting the diet is followed by a good pediatrician to make sure that there still is not a misdiagnosis. Part of the lack of understanding that existed earlier, in the 1960's, was that not all people with high levels of phenylalanine have classical PKU. There are other forms of hyperphenylalanimia that occur that are not as harmful.

I'd like now to contrast PKU with a situation in workplace screening. I think the marker in the HLA system, which is a genetic system, that is considered thus far most predictive of anything is a market called B-27, and it has been suggested as a workplace screening for ankylosing spondylitis.

Mr. GORE. Let me ask you to confirm my understanding of the HLA system. It is a family of substances that are found on the surface of blood corpuscles; is that correct?

Mr. CAPRON. Before we get too technical, I will ask Dr. Sloan to correct anything that I say or any answers that I give.

HLA it is a system which can allow identification, and it has been grouped, and the different markers have been identified. The system is used in many situations in which—for instance, in kidney transplantation and the like—if you can identify similarities their

in HLA groupings, the probability of a good take in a transplant increases.

Mr. GORE. Most of us are familiar with the various blood types, A, O, et cetera, positive and negative factors, and you have a universe of what it does in different blood types. Is that right? But with HLA antigens, the universe of categories is greatly expanding?

Mr. CAPRON. The ABO system is a much simpler set of variations. The HLA system is much more complex.

Mr. GORE. The HLA system essentially identifies smaller substances that are on the surface of blood cells. Is that right, Dr. Murray?

Dr. MURRAY. My understanding is that it is a series of identifiers. Everyone's body can identify foreign matter in the body, and the HLA markers are kind of flags that mark your cell as opposed to somebody else's, and there is a large set of them, and B–27 is one of that set.

Mr. GORE. It is a much more sophisticated analytical tool than the ABO system, and gradually scientists are building libraries of information about human beings associated with different sets of HLA antigens that are present, and there is one of the most promising categories of biochemical genetic screening, and you just said that one of the HLA antigens that is highly predictive is B–27.

Mr. CAPRON. That is right. B–27. You and I ought to do a joint lecture on this sometime.

Mr. GORE. I am a good listener, that is all.

B–27 is a family?

Mr. CAPRON. It is a particular marker in the HLA system.

Mr. GORE. It is a particular HLA antigen?

Mr. CAPRON. It is either present or absent.

Now, if you do screening—again the actual occurrence of ankylosing spondylitis is very rare, maybe 1 in 1,000—so if we screen slightly more than 10,000 people——

Mr. GORE. Tell me what it is associated with first.

Dr. SLOAN. It causes joint problems and mobility problems.

Mr. GORE. Associated with problems in the joints, mobility problems?

Dr. SLOAN. Can be very severe.

[Fig. 2 follows:]

FIGURE 2

SCREENING OF ADULT MALES
FOR ANKYLOSING SPONDYLITIS BY
HLA MARKER B27*

Occurrence of Disorder

Outcome of Screening Test	Present	Absent	Total Tested
Positive	9	1,000	1,009
Negative	1	9,000	9,001
TOTALS	10	10,000	10,010

Sensitivity = 90% (9/10 individuals actually affected are "positive" on screen)
Specificity = 90% (9,000/10,000 individuals actually unaffected are "negative" on screen)
Predictive value = .89% (9/1009 reported "positives" are actually affected; the other 1000 are "false positives")

* This hypothetical testing program is derived from M. Lappe, Ethical Issues Generated by Testing for Genetic Susceptibility to Occupational Hazards or Monitoring for their Mutagenic Effects (1982), p. 30.

Mr. CAPRON. If the test has a 90-percent sensitivity, what that means is that 9 out of the 10 people who have the disorder will show a positive result on the B-27 screen. Nine people out of the 10 expected from 10,000 who have it are found on the screen; 1 is missed.

Likewise, the specificity of the test is also around 90 percent, because out of the 10,000 people who don't have it, 9,000 are shown not to have it.

However, the predictive value of this test, as you can see, is very small because the predictive value is made by comparing the nine who are found to have it, who actually do have it with the thousand who are found to have this marker who don't, in fact, have the disease. If these figures were correct, it would be slightly less than 1 percent.

The difference between this situation and the PKU situation is twofold.

If there is no further test beyond this marker, if the marker is something which, as the chairman just said, is something which these banks of data about HLA markers is beginning to indicate, there is association here, and people say, we can't tell you anything other than association, if there were no followup test, then you are left with 1,009 people who turned out positive on the test, but only 9 of those 1,009 would actually have this condition.

The question that I was asked before about "what do you do?" can be answered as follows: In the case of PKU, you give a treatment to the one child we found who actually had the PKU on followup testing and the mental retardation is avoided.

If the choice here were to exclude the people who turned up positive on this test from the workplace, there is nothing else you can offer them, but simply say, we don't want you working here because we don't want people with your condition. Then you have an additional problem.

Again, I regard that as an ethical issue. It is not simply something on cost-benefit. Cost-benefit might tell an employer whether or not it was ever worth—if he had a particular goal in mind of keeping anybody who turned out positive—whether the cost of running the test was worth it, but then it becomes an ethical choice whether it is permissible to do anything with the results in this case with a 1-percent predictive value.

I use that not to say this is going on now, but merely as an illustration with numbers which you can regard as hypothetical, an illustration of the difference between a screen-like PKU, which has a followup to lead to accurate diagnosis, versus a screen that is making a predictive statement about something which may manifest itself later on with a person without the followup and where the choice is not treatment for that, but exclusion from the workplace. I hope that that helps to explain the terms sensitivity, specificity, predictive value. You also heard about reliability and validity, which relate to other means of describing a test.

Mr. GORE. Well, it is obvious to me that as these libraries of information are expanded, it will not be very long before such tests will be relatively routine.

I could see where that could easily develop, where you would just run a computer analysis of the sample and come up with a printout.

Mr. CAPRON. I would not feel comfortable today talking about all the ways that on a research level that an epidemiologist might use the kind of information that Dr. Lipetz told you about earlier. You could look at that information and look at two people who have had a natural exposure to a high rate of radiation and see whether there is a variation in that population in their chromatid breakage and see whether those people develop cancer at different rates.

Certainly, you are right that people are going to be developing banks of information of this sort and using it, and on a research level I would agree with Dr. Murray's conclusion: It is a valuable research tool, and it is an important tool.

Mr. GORE. Are you familiar with the human protein index, or HPI, that they are developing at Oregon?

Mr. CAPRON. No, I am not. I have been to a meeting where it was described, but I am not familiar with it.

Dr. MURRAY. I have heard of it, but I really don't know much about it.

Mr. GORE. Without objection, we are going to provide some information for the record on this human protein index, which is essentially another library of information being built about humans, that are the subject of these tests, and, as I said before, it is not going to be very long before you can take a small blood sample or a skin sample and run a relatively quick computer analysis and find, and produce, voluminous printout showing percentages of probability that the individual in question will be more or less susceptible to a variety of potential hazards; will be, more or less, likely to develop this particular condition that you were talking about associated with B-27; and if an employer or anybody else is looking for one particular bit of information and gets and happens to discover that the employee is in the 1 percent that is likely to get this condition that you are talking about, I could see where there would be a great temptation to exclude that person from the work force because of health problems that are likely to be present in a short period of time.

Mr. CAPRON. It is important, also, to emphasize that to the extent that this HLA marker, which is presently regarded as the strongest marker of any of them for showing greater susceptibility to disease, has only a 1 percent predictive value, it is already one step beyond Dr. Lipetz' test, which is, at the moment, merely the marker without any proof of its connection to the disease. So there you really have uncertainty times uncertainty. For B-27, it is an uncertainty that which of the 100 people that you take out of the workplace is going to develop the disease as opposed to, is there any connection between this particular marker and a particular condition.

I think I will not finish reading my statement, because——

Mr. GORE. If you can summarize the rest of it.

I apologize for interrupting you.

Mr. CAPRON. I can try to submit something for the record in writing that picks up those two charts.

Dr. MURRAY. There is still a double uncertainty, even with the B–27 screening. The first uncertainty is you will misidentify a lot of people as having B–27 or not.

The second uncertainty is that not all people with B–27 will get ankylosis spondylitis. It is a rare finding. The epidemiologist, as you know from Dr. Gil Omenn.

Mr. GORE. He discussed this question at a previous hearing.

Dr. MURRAY. Recently, he told me there is a 200–fold relative risk increase for people with B–27 to develop ankylosis spondylitis.

It is a rare condition, but people with B–27-positive are more likely to develop it than people without it.

The absolute risk is still very low.

Mr. GORE. Five percent for symptoms that are clear-cut. Perhaps up to 20 percent for suggestive symptoms. Thus, 80 to 95 percent of workers with B–27 would not have and would not be expected to develop ankylosis spondylitis. Early diagnosis and treatment may not even change the course of the disease. Not only would a positive B–27 test not be a basis for excluding workers, but also this lab test would miss the rare patients with some remediable back condition, so the B–27 is not to be recommended for screening, and this is from Gil Omenn.

Mr. CAPRON. I think that the other two things that the Commission's work and conclusions would yield are the emphasis on a need for voluntariness, and—again that there should not arbitrarily be a difference between this field and other forms of genetic testing and screening—the tension between that tradition and the workplace tradition has to be recognized. If there is going to be a separate approach, it ought to be limited as much as possible, for example, by saying that at least the uses and the distribution of the information should be made known to the person. Finally, I believe the Commission would support the conclusions that the findings of a genetic screen ought always to be disclosed to the person.

The notion that this kind of screening can go on and something can be identified is antithetical to the notion that this is a procedure which involves a medical risk to the individual and hand-in-hand with that would be a requirement, I believe, for appropriate genetic counseling to follow up, including conveying to the person how little may be known about whatever the result is.

The mention was made before by Dr. Murray about the tragic consequences that occurred where there were diagnoses of sickle cell traits, a person who has heterozygote, who has one variant gene for sickle cell anemia, and those people were excluded from jobs, and the basis of that misunderstanding, or the people felt stigmatized by that.

I would conclude by saying that the Commission, I believe, thinks that the entire area deserves more attention from educators at all levels and from the Federal Government.

Unfortunately, Federal activity in this area has been decimated by the ending of the National Genetic Diseases Act as part of the reconciliation process last year, and its merger into the maternal and child health block grant, which took the Federal Government's role down to a minimum of its previous level of activity on programs, and hand-in-hand with that goes a lack of ability to support research and education.

I think that we have an area which, if we are going to have public participation, we need an educated public, and people have to be able to understand to participate, and also because of the great effects it may have on their own lives.

[The prepared statement of Mr. Capron follows:]

STATEMENT OF ALEXANDER M. CAPRON, EXECUTIVE DIRECTOR OF THE PRESIDENT'S COMMISSION FOR THE STUDY OF ETHICAL PROBLEMS IN MEDICINE AND BIOMEDICAL AND BEHAVIORAL RESEARCH ON GENETIC SCREENING IN THE WORKPLACE

Good morning, Mr. Chairman and members of the Committee. You have asked me to speak briefly this morning concerning the work of the President's Commission on the ethical and legal implications of genetic screening and counseling. Since this study, one of a number mandated by our enabling legislation (P.L. 95-622), is not yet complete, my comments are based on the Commission's tentative but not yet final conclusions. Indeed, the Commission is considering a draft report on this subject at its meeting on Friday and Saturday this week.

I. RELATIONSHIP OF COMMISSION STUDY TO OCCUPATIONAL SCREENING

Genetic screening and counseling are an increasingly important part of medical practice and public health. In order to avoid duplication of effort, the Commission focused its attention on genetic screening undertaken for reproductive reasons, including prenatal diagnosis, and on screening for early detection of disease, since the Office of Technology Assessment has been conducting a concurrent study of genetic testing in the workplace. It seems important to me, however, especially in an oversight context, not artifically to separate these types of screening. The various reasons for screening and counseling or the settings in which they take place do not in themselves provide bases for the adoption of different policies toward participants. Not only will policies in one area have implications for the policies to be followed in another, but separating them could have particularly significant adverse consequences for the participants. For example, as I will argue in a few moments, it seems

very important for screening of workers for genetic susceptibility to be done in a way that will provide the persons screened with benefits and that is integrated into their general health care. That good is undermined if occupational screening is segregated conceptually from other genetics programs and services. Therefore, I hope it will be helpful for me to share with you some observations drawn from the Commission's work as it seems to relate to occupational genetic testing.

There are two forms of genetic testing in the workplace: (a) programs intended to screen employees for their particular susceptibilty to an occupational hazard that causes illness in some people, and (b) monitoring of employees to discover the mutagenic effects of the work environment. In my remarks I have in mind primarily the former type of testing, for two reasons. First, it is most similar to the types of genetic screening and counseling examined by the Commission; second, mutagenicity surveillance does not seem to me to involve any peculiarly genetic issues. Although much more needs to be learned about the relationship, if any, between changes in chromosomes or in DNA and the occurrence of disease, monitoring for such changes is in theory comparable to other forms of safety monitoring in the workplace that look for any unusually frequent occurrence of health problems among workers. Even the ability of mutagenicity testing to uncover health problems that may be transmitted to subsequent generations (a genetic effect) is not totally unlike other forms of workplace health hazards that may endanger members of an employee's family or other people which whom the employee comes in contact.

The analysis and conclusions that might be drawn from the Commission's work fall into several categories. They are tied together, however, by two common threads. First, we have been struck by the enormous benefits that genetic services can offer people. In focusing on safeguards or limits, no implication is intended that a great deal of knowledge will not be produced of benefit to the participants. Second, decisions about such programs, although they must rest on a sound scientific and economic analysis, are also ethical choices, meaning that aids to decisionmaking (such as cost-benefit analysis, when permissible) fall far short of answering all the difficult questions that must be addressed about the distribution of risks and benefits created by any program. Therefore, it is important for those making decisions about programs, whether they be individual patients, geneticists and other health care providers, or public administrators and legislators, to be aware of the choices that must be made.

II. MAJOR CONCLUSIONS

For the record, I am submitting a copy of the draft conclusions of the Commission which address five areas in which the operation of genetics programs have ethical and legal implications: confidentiality, autonomy, knowledge, personal well-being, and equity. I would be pleased to elaborate on any of those conclusions, but in order to keep this opening statement brief I will just highlight a couple of points.

First, experience with other genetics programs underlines the importance of careful research to arrive at a good understanding of the condition for which tests are being conducted as well as the specificity,

sensitivity, and predictive power of the testing method prior to launching a testing program. Not only is it necessary to avoid premature implementation of a screening procedure but the fact that the research relates to the workplace does not exempt it from usually accepted standards for all experimentation with human beings. (The procedural aspects of these standards are set forth, for Federally supported projects, at 45 CFR 46.) Twenty years ago the first mass genetic screening program was launched with the initial trials of the Guthrie inhibition assay for phenylketonuria (PKU). By testing newborns, the screeners hoped to discover which babies needed a special diet intended to prevent the development of the mental retardation that is one consequence of PKU. The great enthusiasm for this test, which lead rapidly to the adoption of mandatory screening laws in most states, obscured large gaps in understanding both of the disease and of the significance of certain test results. Fortunately, this did not result in major tragic consequences from the screening program, but the Commission found that many leading human geneticists today regard the experience with PKU as a reminder of the need to use greater care in the adoption of screening techniques for other genetic diseases. Moreover, present experience with so-called "PKU mothers" illustrates the need to think through the full consequences of a screening program and plan accordingly.

A second important point to emerge from the Commission's study is the centrality of voluntariness in this field. Mandatory participation is only justified when voluntary testing proves inadequate to prevent serious harm to people, such as children, who are not in a position to make their choice about participating in a program and who are not likely

to receive the necessary testing if participation is left to the voluntary choice of others. The role of voluntariness extends to genetic counseling as well as participation in screening programs. Indeed, genetic counseling is notable--compared to other areas of health care--for its traditional insistence on being "nondirective"--that is, the choices made should truly be those of the person being counselled, not the counselor. This tradition obviously has implications that are at odds with other traditions in the American workplace.

If it is determined that the same level of voluntariness is not compatable with the workplace, I believe the Commission's study would lead to three conclusions that relate to the principles of respect for persons and of beneficence. First, the uses of the information ought to be limited to the extent possible and confidentiality protected through appropriate safeguarding steps. Unfortunate experiences with sickle cell testing in the early 1970's--including apparent breaches of confidentiality and confusion of sickle cell disease with carrier status--serve as reminders of what can happen when programs are launched without attending to those concerns. Second, whatever uses of screening results are found to be necessary, a person who undergoes occupational genetic screening ought to be fully informed about them. In that event, the choice to expose oneself to whatever risks accompany the screening would at least be knowingly made even if the voluntariness of the choice is limited because screening has been made a condition of employment.

Finally, the Commission's work would I believe support the conclusion that the findings of a screening program ought always to be made available to the person screened along with appropriate counseling to help the

person to understand the meaning of the results. In other words, part of the justification for screening, even in the workplace, is that it can provide information that may be of benefit to those who are screened, either in their own health care or in reproductive decisionmaking. Thus, it would be inappropriate to launch a program of workplace screening before provision has been made for the necessary follow-up on the screening results, including not only any further tests necessary to convert an initial screen into a definitive finding but also the availability of trained genetic counselors.

Finally, the Commission has been impressed with the need for better public understanding of genetics. People who are presented with a screening program will need to realize that a biomedical scientist cannot simply look at a drop of blood of other fluid or cell sample from a person and decipher the person's genes. The number of diseases for which screening is possible today is still relatively limited, though growing. (In most cases, a test conducted for one purpose will not yield information about other genetic conditions.) Furthermore, even were it possible to make a "gene map" of a person, the connections between genes and most characteristics and propensities is not known. (Many of the things of greatest interest to people are multifactorial, involving the interaction of a number of genes and the environment, rather than being determined by variation in a single gene, like Tay-Sachs disease or cystic fibrosis.) The ability of people to appreciate just what screening can and cannot accomplish, in the context of a specific workplace or other screening program, would be enhaced by better elementary and secondary education in mathematics and science, particularly genetics.

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Attachment to Mr. Capron's Testimony

SUMMARY OF COMMISSION'S DRAFT CONCLUSIONS

The Commission's basic conclusion is that programs to provide genetic education, screening, and counseling provide valuable services when they are established with concrete goals and specific procedural guidelines founded on sound ethical and legal principles. Its major conclusions fall into five categories.

A. Confidentiality:

1. Genetic information should not be given to unrelated third parties, such as insurers or employers, without the explicit consent of the person screened.

2. Private and governmental agencies that utilize data banks for genetics-related information should require that stored information be coded whenever that is compatible with the purpose of the data bank.

3. Overriding requirements of confidentiality, genetic information may be released to relatives (or their physicians) if and only if reasonable efforts to elicit voluntary consent to disclosure have failed, identifiable individuals would suffer serious harm if the information is not disclosed, there is a high probabilty both that the harm will occur if the information is withheld and that the disclosed information will actually be used to avert the harm, and appropriate precautions are taken to ensure that only the genetic information needed for diagnosis and/or treatment of the disease in question is disclosed.

- When it is known in advance that the results of a proposed screening program could be uniquely helpful in preventing serious harm to the relatives of anyone screened, it may be justifiable to make access to that program conditional upon prior agreement to disclose the results of the screening.

4. Law reform bodies, working closely with genetic professionals and organizations interested in adoption policies, should urge changes in adoption laws so that information about serious genetic risks can be conveyed to adoptees or their biological families. Genetic counselors should mediate the process by which adoptive records are unsealed and newly discovered health risks are communicated to affected parties.

B. Autonomy:

5. Mandatory genetic screening programs are only justified when voluntary testing proves inadequate to prevent serious harm to the defenseless, such as children, that could be avoided were screening performed.

- The goals of "a healthy gene pool" or a reduction in health costs do not justify compulsory genetic screening.

6. Professionals should generally promote and protect patient choices to undergo genetic screening and counseling, although the use of amniocentesis for gender selection should be discouraged.

- Genetic screening and counseling are medical procedures that may be elected by an individual on the basis of personal choice when the individual desires information to aid in making personal medical and reproductive choices.

- In finding that the value of the information provided by genetic screening and counseling would be diminished were the reproductive choices available restricted, the Commission merely presents a factual conclusion that is not intended to involve it in the national debate over abortion.

C. Knowledge:

7. Disclosure of incidental findings, such as nonpaternity, or of sensitive findings, such as diagnosis of an XY-female, should begin with a presumption in favor of disclosure, while still providing careful protection of the client's other interests as determined on a case-by-case basis. When full disclosure is not made, accurate information about recurrence risk should at least be provided.

8. Efforts to develop genetics curricula for elementary, secondary and college settings and to work with educators to incorporate appropriate materials into the classroom are commendable. The knowledge imparted is not only important in itself but also promotes values of personal autonomy and informed public participation.

9. Organizations such as the American Association of Medical Colleges, the American Medical Association, and the American Nursing Association should encourage the upgrading of genetics curricula for professional students. Professional educators, working with speciality societies and program planners, should identify effective methods to educate professionals about new screening tests. Programs to train health professionals in technical, social, and ethical aspects of genetic screening deserve support.

D. Well-being:

10. A genetic history and, where appropriate, genetic screening should be required of men donating sperm for artificial insemination; professional medical associations should take the lead in identifying what genetic information should be obtained and in establishing criteria for excluding a potential donor.

- Records of sperm donors are necessary, but should be maintained in a way that preserves confidentiality to the greatest extent possible.
- Women undergoing artificial insemination should be given genetic information about the donor as part of the informed consent process.

11. Screening programs should not be undertaken unless accurate results will be produced routinely and a full range of prescreening and follow-up services are available.

- Funding agencies should support pilot studies of promising new screening techniques. Screening programs should not be implemented until the test has first demonstrated its value in well-conducted pilot studies; when products involved in the testing are subject to government regulatory review, agencies should require such pilot studies as a pre-requisite to approval.
- Community leaders and community-based organizations should play an integral part in planning screening programs.

- States should consider establishing a review group with professional and public members to oversee genetic services.
- The possibility of follow-up studies should be seriously considered for each genetic screening and counseling program.

E. Equity:

12. Access to screening may take account of the incidence of genetic disease in subpopulations without violating principles of equity, justice, and fairness.

13. As limitations on access move from a research context to implicit or explicit policies on the availability of a genetic service, they should be subjected to review by a broadly based process that is responsive to the full range of relevant considerations, to changes in operative facts over time, and to the needs of the groups excluded.

- The time has come for such a review of the common medical practice of limiting amniocentesis for "advanced maternal age" to women 35 years or older.

14. Determination of issues such as which groups are at high enough risk for screening or at what point the predictive value of a test is sufficiently high require ethical as well as technical analysis.

15. Cost-benefit analysis can make a useful contribution to allocational decisionmaking, provided that the significant limitations of the method are clearly understood; it does not provide a means of avoiding difficult ethical judgments.

Mr. GORE. Thank you very much for excellent testimony.

Mr. Shamansky.

Mr. SHAMANSKY. Thank you, Mr. Chairman. First of all, I wish to comment that I have been actually fascinated today by the quality of testimony.

Mr. Chairman, it is a marvelous presentation.

I am responding—I keep mentioning I am a lawyer; you have been a lawyer for 30 years; you think in these terms, but the thing that keeps worrying me is the fact that our common-law process is going on, and these are not isolated situations.

We have people who are worrying about legitimately what happens if I am sued. That is not necessarily bad if they are being hurt someplace. I am being hurt; why didn't you protect me?

Those are very human things, and the law is designed properly in our system to help someone who is hurt.

And so, therefore, we—I mean I always, maybe by my conditioning, say, maybe what happens if, and it is difficult for me to say well, the odds are very small, but if a client comes into your office, and he is devastated, well, he fell out on the end of this percentage thing, and, therefore, you are statistically insignificant, but the person is certainly significant certainly to himself, and the law tries to accommodate you, but we are trying to set these overall standards.

It is not just a matter of science, and just a matter of ethics, because I really think the law addresses both of those and makes it possible for society to live with itself.

The testimony has hit on many of these points.

In Dr. Murray's testimony, I noted on page 3 your comment in your last paragraph, the sentence says rarely will the news be as catastrophic as the imagination might fear, but there is a fear?

Dr. MURRAY. Yes, if you tell somebody you have a genetic anomaly, which we have, any number of us—Dr. Sloan said three to seven fatal anomalies—the public is very frightened. I don't know why.

People are scared about certain things more than they need to be perhaps, and genetics conjures up that fear; but with good counseling, and we have models how to do this now, you can allay that fear.

Mr. SHAMANSKY. Your next sentence is significant. You say, unfortunately good medical genetic counseling is probably less common than it should be and individuals are and will be misinformed and uninformed; so my question is, Doctor, what is the response that you see in the medical profession to allay these fears?

You are saying that good counseling is less than it should be. What is being done to make sure it gets better?

Dr. MURRAY. Everyone getting adequate counseling.

How to do that would be the same way one tries to institute or enforce good practice in any profession.

Mr. SHAMANSKY. Do you see it is being done by the, I will say, the American Medical Association? And I am not picking on them. Well, organized medicine?

Dr. MURRAY. I see a serious effort on the part of people involved in human genetics counseling to take that responsibility seriously.

Mr. SHAMANSKY. I am talking about overall is the profession aware of genetic counseling? Not are the counselors doing a good job.

Mr. CAPRON. A few years ago, the National Academy of Sciences had a committee on which I served on the subject of genetic screening. We did a study of the general medical population, and we found that although among recent graduates of medical school, there was an increased knowledge of genetics, as of the midseventies, the percentage of physicians who could correctly identify genetic diseases and would be in a position to take appropriate steps and appropriate counseling was actually quite small.

In the last decade, there has been increased attention and research and training grants for people in genetics through the National Institutes of Health. Those have been now severely cut back as a result of the reconciliation process last year, and——

Mr. SHAMANSKY. They were what?

Mr. CAPRON. Cut back, so they will be less federally supported.

Mr. SHAMANSKY. Someone making up for it from the non-Federal level?

Mr. CAPRON. In any area of medicine I believe you will see some response.

Mr. SHAMANSKY. I am not talking about some.

Mr. CAPRON. I doubt, sir, that there is as much being made up as the diminution of training grants for people in medicine and Ph. D.'s to become trained medical geneticists.

There is attention to this area and programs to train people, people receiving a master's degree, master of science in genetic counseling, at a number of institutions, and the American Society of Human Genetics has established standards and tests.

Mr. SHAMANSKY. It is your opinion over all that it will be less of an effort than we have enjoyed heretofore, as a matter of opinion?

Mr. CAPRON. I am cautious on this, because I don't have the current figures on training grants for this year.

My impression would be certainly there is going to be less as a result of the drop in Federal funding, yes. In the long run, whether the demand is going to draw people into this field as it does into any medical specialty, I could only speculate. We don't have to give a lot of training grants to certain medical specialties to draw people to them because they know the demand is there. This is still a fairly specialized form of medical practice, largely practiced out of the 270 or so medical genetic centers, but compared to a decade ago, it is an order of magnitude larger. It is a field that is growing very rapidly, and the real question is disseminating this information outside that group of specialists.

Mr. SHAMANSKY. What is the progress in that area?

Mr. CAPRON. As of a few years ago, that had not gone very far, and whether we ought to have another study to see if the medical profession is any more aware of this——

Mr. SHAMANSKY. Are you going to write the AMA a letter on that?

Mr. CAPRON. Are you?

Mr. SHAMANSKY. That is a good question, which is one of the reasons for these hearings, and I am not picking on the AMA, but we think of the——

Mr. CAPRON. It just sounds that way.

Mr. SHAMANSKY. Unfortunately, it does. That is not my intention. I don't know how else to reach the broadest expanse of practicing physicians.

I think we can address properly the National Institutes of Health and ask them, what are they doing to get the information out?

We could give the AMA, or whatever particular committee they have, and I am sure they do have the benefit of our hearings here, our report; but you are onto something serious, and I hope we are.

Mr. CAPRON. Another important line of inquiry would be Association of American Medical Colleges, because it is certainly true today genetics is more broadly taught. Whether it is true every medical student receives adequate exposure as part of their training to that, so that the next generation of physicians——

Mr. SHAMANSKY. I have no illusions about my absolute qualifications to judge whether or not the medical student is or is not, but what I am concerned about are the medical colleges and their associations concerned for their own members and their own students, and is the profession, itself, concerned about these areas?

That is the way we would get at it.

Mr. CAPRON. Anticipating one thing that will come up which I know from our studies and our attempts to have some of the more human relations aspects of medical practice emphasized more in medical schools, the answer is that, as you hear constantly in this committee and other committees of Congress, medical science is growing by leaps and bounds, and there is great competition in the training of physicians for time to get across information which 5 years ago did not exist.

Mr. SHAMANSKY. Doesn't that, of necessity, push you into more and more specialties?

Mr. CAPRON. It does, but then the answer comes back, if you go and look at the general medical population, and ask them about genetics, the fact that very few know the answers and don't recognize genetic diseases, it comes back to that is why they had to have all their time in neurology, and so forth.

Mr. SHAMANSKY. It is a dilemma.

Mr. CAPRON. Of course, it is.

Mr. SHAMANSKY. Page 4 of Dr. Murray's testimony, research, you say for perhaps a handful of genetic factors, we have the beginnings of piece No. 1, and that is where there are certain genetic conditions which translate themselves into illnesses. Correct?

Dr. MURRAY. That would be a case. For example, there was an incident in a dynamite factory in Israel, where workers who manufactured TNT and who had a particular genetic anomaly whose name I am not sure of at this moment, fell ill, and in the diagnosis, the clinical workup of those individuals, they were found to have this genetic condition in common. So that is a clinical indication that there might be some connection between that anomaly, that workplace exposure—TNT as a solvent—and a particular disease.

Mr. SHAMANSKY. That raises all those ethical questions as to what you do when another person with that genetic factor comes to apply for a job?

Dr. MURRAY. We have not even gotten to that point yet, because in this case you have to ask, how did that exposure come about?

Was it an accident, a sudden, say, a hundredfold increased exposure, an exposure under no normal working conditions?

Mr. SHAMANSKY. Doctor, are there any genetic factors which translate illness, given certain conditions?

Dr. MURRAY. Oh, of course.

Mr. SHAMANSKY. OK. All I am saying is, if that exists, then all of these questions are, these challenges and legal questions arise.

What do you do?

I think it is legitimate for the employer to say, hey, how much, what responsibility do I have toward the prospective employee and toward myself, because he may turn around someday and sue me because I did not exclude him, but these tests were available, and I knew the conditions existed in my place of employment.

Dr. MURRAY. In every case we don't know of current exposure levels to any substance linked to any genetic anomaly with leading to disease silly exceptions like the hemophiliac butcher.

Would you let an Albino work as a farmworker? Probably not.

Mr. SHAMANSKY. Dr. Sloan was talking about it. Is it sickle cell trait? And he said in all fairness, I don't think he should be an airline pilot because of——

Dr. MURRAY. The Air Force disagrees.

They have changed their mind on that a couple of times.

There was a case of a number of black candidates at the Air Force Academy on high altitude maneuvers who had some kind of reaction, from what I understand; but here we really need someone who knows the details of the case, and we don't know if every person had sickle cell traits.

Dr. SLOAN. Some would and some wouldn't.

Dr. MURRAY. Even the ones who fell sick, we don't know for a fact that they had sickle cell traits.

Also, that was under extreme conditions.

Mr. SHAMANSKY. I understand. Dr. Sloan clearly mentioned the altitude and the pressurized cabin part.

In your statement, there are no sure connections between a genetic trait and absence or presence, as the case may be?

Dr. MURRAY. Three factors: the trait, the workplace exposure, that is, exposures that are currently available in our workplaces and disease—and the answer is, there is really not much.

Mr. SHAMANSKY. I worry, as a lawyer.

You say not much but some.

Dr. MURRAY. The ankylosis spondylitis link to B–27 is the only one I am aware of, where there is even a respectable minimum of that.

Mr. SHAMANSKY. Without determining this finally?

Mr. CAPRON. G–6–PD is the other example often cited?

Dr. MURRAY. G–6–PD at the levels that American workers experience will fall short.

Mr. SHAMANSKY. Personally, my approach to these things is based on the best scientific evidence possible, and yet the whole dilemma here is there are these very human and ethical and legal factors, and it is that interrelationship, and it is very, very difficult, I find, and that is why you are an anesthesist, help people think their way through these things, but it is going to be a more difficult challenge. We seem to be statistically becoming a more li-

tigious society, and I am not sure that is necessarily bad if that is the struggle for justice for people in our society.

Certainly it is going to be a continuing challenge among legislators, lawyers, scientists, and businessmen, how these things sort themselves out.

I enjoyed your testimony very much.

Thank you, Mr. Chairman.

Mr. GOSS. Thank you.

The OTA did a survey, found biochemical screening for sickle cell, G-6-PD, SAT, methemoglobin reductase, red blood cell serum disorders, liver detoxification, and immune system markers, and in the cytogenetic area, they were looking for chromosomal aberrations and sister chromatid exchange, which is interesting, and leads me to a question for you, Dr. Murray.

You have produced, beginning on page 8 of your testimony, a very thoughtful list of questions which ought to be addressed by anyone considering exclusion from the workplace on the basis of genetic screening: How many people have the anomaly? What is the relative risk and the absolute risk? A number of false negatives and false positives, the number of people that are misidentified, how many jobs involved, the character of the illness in question, how solid is the evidence; does the screening program concentrate on groups with a history of having suffered discrimination, and how does it compare in cost-effectiveness to other means of reducing work-related disease?

All of those questions are very sensitive questions, and I would recommend that list to anyone in industry looking at this area.

There is one question that is not on the list, and maybe because it is a legal question and not strictly speaking to an ethical question, and that is, who makes the choice? Who is making the choice? Who is asking these questions, and who is answering these questions?

By the standards that the two of you have laid out for us, and by the standards laid out by other witnesses here today, there does not seem to be a justifiable reason for using these tests in free employment settings at all now, because they are not accurate enough to be used.

Yet the evidence indicates that they are being used, and that leads me to believe that the questions—who makes the choice and who asks the questions?—may be at least as important as all of the ethical considerations that are involved.

How would you deal with that, Dr. Murray? It seems to me that it is possible that if you have an interested party with specific legal and economic interests that are in opposition to at least in some respects the interests of the person who is the subject of the test, then that will produce a consistent—I don't want to use the word bias—but a consistent pattern in the responses to all of these very sensitive ethical questions.

Dr. MURRAY. Well, first of all, you could not have said anything more important when you said that in the end, who makes the decision, is going to be of essential importance; that is absolutely correct.

I suppose it should be on the list, but it isn't on the list for a variety of reasons. It is a question I can't answer easily.

In an ideal world, we give that decision to a person who is in a position where they are not biased, where their goal is the protection of the worker, and with reasonable consideration of the social costs of the various policies we have available.

Now, that is, I assume, what the committee is up to. The committee's interest is in balancing these various competing interests in the most equitable way possible.

The questions I have posed are objective ones, objectively answerable, factual questions. How many jobs are involved? You can find that out.

How many people? You can find that out.

How solid is the evidence? That requires judgment.

These are the factual questions that underlie the choice which is precisely the one you point out.

Mr. GORE. Well, thank you for that response.

I think, as these tests become more sophisticated and more widely used, I think that it is inevitable that at some point there be publicly agreed-upon guidelines for the use of such tests, so that employers don't make the decisions in every case about what is fair and not fair, because, as we see from the record to date, there are intense pressures on employers to use these tests even when they are only marginally predicted, and there will be similar pressures to answer these kinds of sensitive questions in ways that will sometimes lead to results unfair to job applicants and employees. I think the kind of list that you have produced here, and the kinds of questions that you have provided, Mr. Capron, and our other witnesses today, and certainly OTA, will be extremely useful in fashioning the guidelines that perhaps the Administrator of OSHA will use in looking at whether these tests are accurate or not, in forming legislative history for the Rehabilitation Act changes, if they are considered, to assist you in deciding when it is fair and unfair to use such tests.

Mr. CAPRON. Mr. Chairman, could I respond to the question you asked Mr. Murray, the following way? It would seem to me worthwhile for you to inquire not only in industry, but also with the Department of Defense. Back in 1973, a committee at the National Academy of Sciences—at the request of the Department of Defense—undertook a study of the hemoglobinopathies, including thalessemia and G-6-PD, and recommended a program for the evaluation of their status in the Armed Forces, and you could do well to find out what steps have been taken and whether the kinds of questions that Mr. Murray asked are being asked there.[1]

Beyond that, I would disagree, and I find myself in a position of giving unsolicited legal advice, but I might disagree with Mr. Karny and the OTA that at the kinds of levels that one is talking about here of the predictability of the tests, that there would be any likelihood that a worker who was injured and who had not been screened, where an employer had gone through the kinds of thinking that Dr. Murray just recommended and decided it is not now appropriate to use this test because it will give biasing and

[1] Ad Hoc Committee on S-hemoglobinopathies, The S-hemoglobinopathies—An evaluation of their status in the Armed Forces, national Academy of Sciences, Washington, D.C. (February, 1973.)

confusing results, that the likelihood that there will be any basis for an action in negligence as opposed to their worker's compensation claim for the injury that occurred——

Mr. SHAMANSKY. That is the thing I am concerned with.

Mr. CAPRON (continuing). The pressure coming from the law on that side is likely to be very small.

The pressure is more likely to be coming from misguided economic conclusions from an employer, if an employer thinks that he has a 90 percent chance of being wrong, but a 100 percent chance of being right in keeping somebody out who could be very ill, he may think if I have a large workforce, all of them are equally qualified.

Mr. GORE. I think that what Mr. Karny said was, the more predictive a test becomes, the more the legal pressure on the employer becomes as a result of employees moving outside the workmen's compensation statutes.

Mr. CAPRON. It would become an extreme example of wrongdoing on the part of the employer to take a worker outside the workers' compensation area. It is against the third party, the manufacturer of the machinery or the like that malfunctions, that workers have sued outside of worker's comp. Certainly, a testing company that came in and did a wrong test, that might be an example of a non-employee-employer relationship that could get out from under workers' compensation.

There are more likely to be pressures from the Office of the Comptroller in a corporation than the Office of the General Counsel for premature adoption of these tests.

Mr. SHAMANSKY. What would inspire the Comptroller?

Mr. CAPRON. If you have 10,000 equally qualified workers, and someone who comes in and says, we don't know it for sure yet, but we think we can eliminate 90 percent of the people who are going to get these joint diseases and pin them on us, if we use the test and the test does not cost us that much.

Mr. SHAMANSKY. You can't go on that basis; that would be an unfair discrimination.

Mr. CAPRON. Yes, I agree that if the Congress is looking at that problem, they may say that is a wrong thing to do, but I would not think that the person who is urging the employer to do that is as likely to be his general counsel as it is to be his treasurer, who says if we got 10,000 equally qualified people and get rid of a thousand of them, if even only 9 out of 1,000 will get sick——

Mr. SHAMANSKY. I understand that you are the lawyer.

You see, we are the rational guys.

Dr. MURRAY. Nor is the pressure likely to come from the medical director of the company.

Mr. GORE. Treasurers more likely have more influence than either of the other two.

There are two recent cases under workmen's comp, one in California and one in Illinois, involving asbestos. They were allowed to go outside.

There is, in fact, growing pressure on corporations in this area, and the point I wanted to make earlier was, I did not think what you said was really that different from what Mr. Karny said. What

he was saying, as they become more predictive, then the legal concerns grow on the part of the corporation.

Mr. KARNY. Yes. Mr. Capron misunderstood what I was saying. I was taking the hypothetical situation where the tests were highly predictive and saying, in that context, it may be negligent for an employer to do a test and then place the employee in a high-risk environment without any other protection.

Now, of course, there are other considerations. You still have worker's compensation. Therefore, the employee may not be able to sue the employer and recover damages. But looking only at the legal definition of negligence, the employer probably would be negligent in my hypothetical case.

Mr. GORE. Thank you.

Mr. CAPRON. I would agree with that, but I would underline the difficulty of bringing the suit, and it is important to look at where the interest in this is going to come from. The concern with premature judgments—which is the real conclusion—is a very well-taken concern, and I hope, whether it is under existing statutes or with further encouragement, that people who are concerned with the labor situation in this country will take note.

Mr. GORE. Thank you very much. This is the third hearing in a series that we have had on this subject, and, as I said at the outset, it is our hope that by looking at issues like this that are on the horizon, we will be able to prove our country's ability to wrestle with the questions presented by genetic screening before the problem develops into a form that makes it more difficult to deal with, and you two have contributed a great deal to that effort, and I wish to thank you on behalf of the subcommittee, and I wish to thank all of our witnesses who have appeared today.

With that, I will declare the hearing adjourned.

[Whereupon, at 1:25 p.m., the subcommittee adjourned, to reconvene subject to the call of the Chair.]

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